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HOLOGIC, INC., CYTYC CORPORATION and HOLOGIC L.P.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION,
and HOLOGIC L.P.,

Plaintiffs,

vs.

SENORX, INC.,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C08 00133 RMW (RS)

**DECLARATION OF KATHARINE L.
ALTEMUS IN SUPPORT OF PLAINTIFFS'
OPENING CLAIM CONSTRUCTION
BRIEF (PATENT L.R. 4-5(a))**

Markman Hearing

Date: June 25, 2008

Time: To Be Set

Room: Courtroom 6, 4th Floor

Judge: Hon. Ronald M. Whyte

1 I, Katharine L. Altemus, declare that I am an associate in the law firm of Howrey LLP and a
2 member of the Bar of this court, and I serve as one of the outside counsel for Plaintiffs Hologic, Inc.,
3 Cytyc Corporation and Hologic LP. The following declaration is based on my personal knowledge,
4 and if called upon to testify, I could and would competently testify as to the matters set forth herein.

5 1. Attached hereto as Exhibit A is a true and correct copy of United States Patent No.
6 5,913,813.

7 2. Attached hereto as Exhibit B is a true and correct copy of United States Patent No.
8 6,413,204.

9 3. Attached hereto as Exhibit C is a true and correct copy of United States Patent No.
10 6,482,142.

11 4. Attached hereto as Exhibit D is a true and correct copy of Defendant and
12 Counterclaimant Cytyc Corporation's Opening Claim Construction Brief (Pat. L.R. 4-5(a)), filed in
13 *Xoft v. Cytyc Corporation, et al.*, United States District Court, Northern District of California, Case
14 No. CV-05-05312 RMW on November 9, 2006, Docket No. 48.

15 5. Attached hereto as Exhibit E is a true and correct copy of Order Denying Plaintiffs'
16 Motion for Preliminary Injunction (Unredacted Version) Filed Under Seal in the within action on April
17 25, 2008, Docket No. 110.

18 6. Attached hereto as Exhibit F is a true and correct copy of Claim Construction Order,
19 filed in *Xoft v. Cytyc Corporation, et al.*, United States District Court, Northern District of California,
20 Case No. CV-05-05312 RMW on April 27, 2007, Docket No. 109.

21 7. Attached hereto as Exhibit G is a true and correct copy of Plaintiffs' Notice of Motion
22 and Motion for Preliminary Injunction filed under seal in the within action on February 6, 2008,
23 Docket No. 8.

24 8. Attached hereto as Exhibit H is the Declaration of Lynn J. Verhey, Ph.D. In Support Of
25 Plaintiffs' Proposed Construction Of Claim Terms, Phrases And Clauses, with exhibits A, B, and C
26 thereto, signed on May 21, 2008.

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28

EXHIBIT A



United States Patent

Williams et al.

[19]

[11]

Patent Number: 5,913,813

[45]

Date of Patent: Jun. 22, 1999

[54] **DOUBLE-WALL BALLOON CATHETER FOR TREATMENT OF PROLIFERATIVE TISSUE**

[75] Inventors: **Jeffery A. Williams**, Baltimore, Md.;
Christopher H. Porter, Woodinville, Wash.;
Jeffrey F. Williamson; **James F. Dempsey**, both of St. Louis, Mo.;
Timothy J. Patrick; **James B. Stubbs**, both of Alpharetta, Ga.

[73] Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, Ga.

[21] Appl. No.: 08/900,021

[22] Filed: Jul. 24, 1997

[51] Int. Cl.⁶ A61N 5/00

[52] U.S. Cl. 600/3

[58] Field of Search 600/1-8

References Cited

U.S. PATENT DOCUMENTS

3,324,847 6/1967 Zoumboulis .

5,106,360	4/1992	Ishiwara et al. .	
5,429,582	7/1995	Williams .	
5,611,767	3/1997	Williams .	
5,662,580	9/1997	Bradshaw et al.	600/3
5,782,742	7/1998	Crocker et al. .	
5,785,688	7/1998	Joshi et al. .	

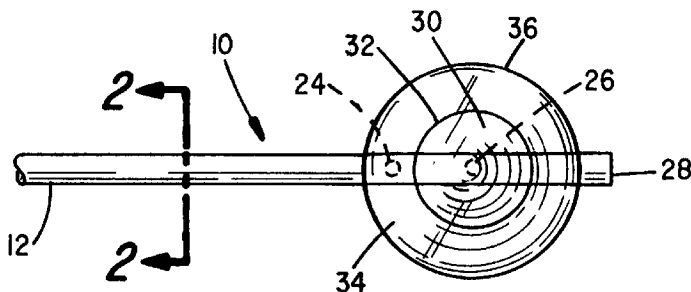
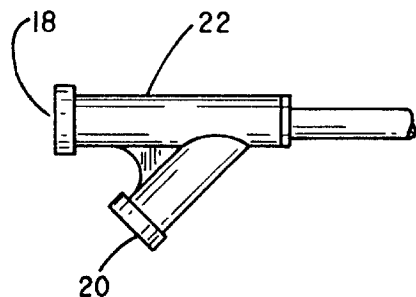
Primary Examiner—John P. Lacyk
Attorney, Agent, or Firm—Nikolai, Mersereau & Dietz, P.A.

[57]

ABSTRACT

An instrument for use in brachytherapy comprises a concentric arrangement of inner and outer distensible, spherical chambers disposed near the proximal end of a catheter body where one of the chambers is made to contain a radioactive material with the other chamber containing a radiation absorptive material, the apparatus functioning to provide a more uniform absorbed dose profile in tissue surrounding a cavity created by the removal of a tumor. An alternative embodiment includes non-spherical inner and outer chambers whose respective walls are spaced equidistant over the entire surfaces thereof.

13 Claims, 2 Drawing Sheets



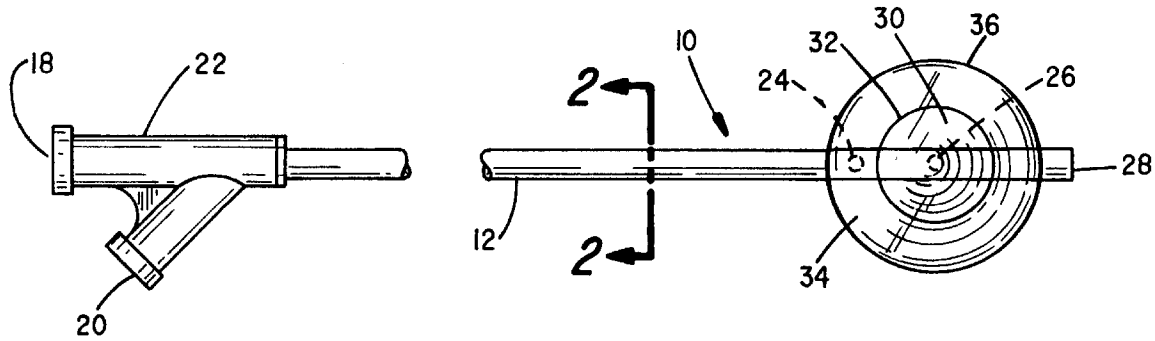


FIG. 1

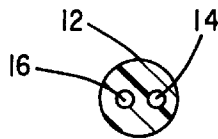


FIG. 2

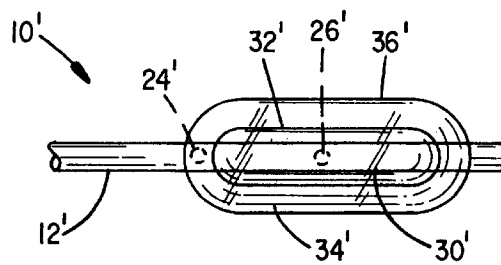


FIG. 3

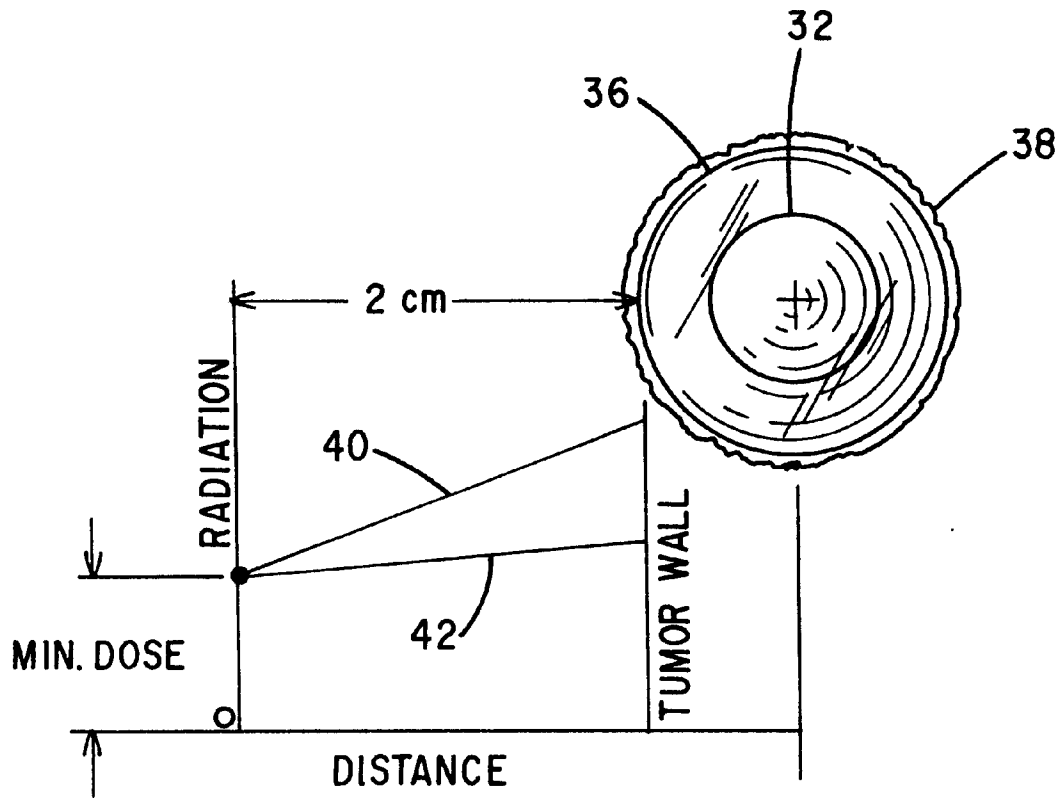


FIG. 4

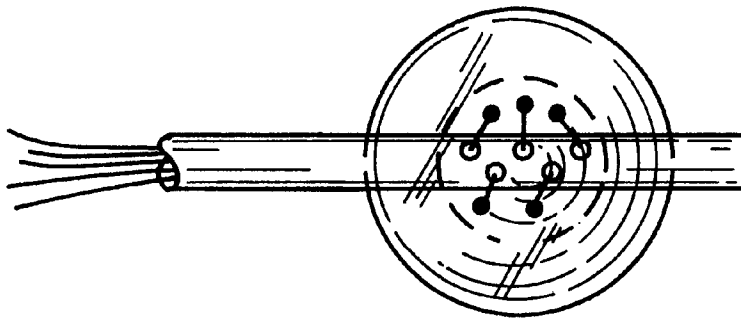


FIG. 5

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DOUBLE-WALL BALLOON CATHETER FOR TREATMENT OF PROLIFERATIVE TISSUE

BACKGROUND OF THE INVENTION

I. Field of the Invention

This invention relates generally to apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radioactive material and/or radiation emissions.

II. Discussion of the Prior Art

In the Williams U.S. Pat. No. 5,429,582 entitled "Tumor Treatment", there is described a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the margins surrounding the excised tumor. In accordance with that patent, there is provided a catheter having an inflatable balloon at a distal end thereof to define a distensible reservoir. Following surgical removal of a tumor, say in the brain or breast, the deflated balloon may be introduced into the surgically-created pocket left following removal of a tumor and then the balloon is inflated by injecting a fluid having radionuclide(s) therein into the distensible reservoir, via a lumen in the catheter.

When it is considered that the absorbed dose rate at a point exterior to the radioactive source is inversely proportional to the square of the distance between the radiation source and the target point, tissue directly adjacent the wall of the distensible reservoir may be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a site 0-3 cms away from the wall of the excised tumor. It is desirable to keep the radiation in the space between that site and the wall of the distensible reservoir as uniform as possible to prevent over-exposure to tissue at or near the reservoir wall. In treating other cancers, such as bladder cancer, where the neoplastic tissue is generally located on the bladder surface, deep penetration is unnecessary and to be avoided.

A need exists for an instrument which may be used to deliver radiation from a radioactive source to target tissue within the human body of a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target.

SUMMARY OF THE INVENTION

We have found that it is possible to deliver a desired radiation dose at a predetermined radial distance from a source of radioactivity by providing a first spacial volume at the distal end of a catheter and a second spacial volume defined by a surrounding of the first spatial volume by a polymeric film wall where the distance from the spatial volume and the wall is maintained substantially constant over their entire surfaces. One of the inner and outer volumes is filled with either a fluid or a solid containing a radionuclide(s) while the other of the two volumes is made to contain either a low radiation absorbing material, e.g., air or even a more absorptive material, such as an x-ray contrast fluid. Where the radioactive material comprises the core, the surrounding radiation absorbing material serves to control the radial profile of the radioactive emissions from the particular one of the inner and outer volumes containing the radionuclide(s) so as to provide a more radially uniform radiation dosage in a predetermined volume surrounding the

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outer chamber. Where the core contains the absorbent material, the radial depth of penetration of the radiation can be tailored by controlling the core size.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. 1 is a side view of an apparatus for delivering radioactive emissions to body tissue;

FIG. 2 is a cross-sectional view taken along the line 2—2 in FIG. 1;

FIG. 3 is a fragmentary side view of an apparatus for administering radiation therapy in accordance with a second embodiment;

FIG. 4 is a graph helpful in understanding the operation of the apparatus of the present invention; and

FIG. 5 depicts a further embodiment of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring first to FIG. 1, there is indicated generally by numeral 10 a surgical instrument for providing radiation treatment to proliferative tissue in a living patient. It is seen to comprise a tubular body member 12 having first and second lumens 14 and 16 (FIG. 2) extending from proximal ports 18 and 20 in a molded plastic hub 22 to inflation ports 24 and 26 formed through the side wall of the tube 12 and intersecting with the lumens 14 and 16, respectively.

Affixed to the tubular body 12 proximate the distal end 28 thereof is an inner spatial volume 30 which may be defined by a generally spherical polymeric film wall 32. The interior of the chamber 30 is in fluid communication with the inflation port 26. Surrounding the spatial volume 30 is an outer chamber 34 defined by an outer polymeric film wall 36 that is appropriately spaced from the wall 32 of the inner chamber 30 when the two chambers are inflated or otherwise filled and supported. Chamber 34 encompasses the inflation port 24.

The embodiment of FIG. 1 can be particularly described as comprising two spherical chambers 30 and 34, one inside the other. In accordance with a first embodiment of the invention, the outer chamber 34, being the volume defined by the space between the inner spherical wall 32 and the outer spherical wall 36, may be filled with air or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. The inner chamber 30 is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles or other therapeutic rays.

Those skilled in the art will appreciate that instead of having the inner spatial volume 30 defined by a generally spherical polymeric film wall as at 32, the catheter body member 12 may have a solid spherical radiation emitting material in which event that solid sphere would be surrounded with the outer spherical wall 36 with the spatial volume therebetween occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

It is further contemplated that instead of having the inner spatial volume comprising a single solid sphere, it may instead comprise a plurality of radioactive particles strategically placed within the inner spatial volume so as to radiate

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in all directions with a substantially equal intensity. FIG. 5 illustrates a catheter having the inner spatial volume occupied by a plurality of radioactive beads that are mounted on the distal ends of a plurality of wires that are routed through the catheter body and exit a plurality of ports formed through the wall of the catheter body and reaching the lumen. This arrangement allows the exact positioning of the individual radiation sources to be positioned so as to generate a desired resultant profile.

It is not essential to the invention that the chambers 30 and 34 have spherical walls, so long as the spacing between the wall of the inner chamber and the wall of the outer chamber remain generally constant, such as is illustrated in FIG. 3.

Referring to FIG. 4, there is shown the two concentric spherical chambers of FIG. 1 defined by inner spherical wall 32 and outer spherical wall 36 disposed within the margin 38 of a surgically excised tumor. It is desired that the radiation emitted from the core 32 be capable of delivering a certain minimum dose absorbed at a location approximately 0–3 cms from the margin 38. Curve 40 is a plot of absorbed dose vs. radial distance that would be obtained if the inner chamber defined by spherical wall 32 was not present and the entire volume of the spherical chamber defined by wall 36 were filled with the radioactive fluid. Plot 42 reflects the absorbed dose distribution as a function of radial distance when the radioactive fluid is contained within the inner chamber and is surrounded by either a gas or a more radiation absorbing material. Comparing the plots 40 and 42, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2 cm site and the wall of the outer balloon is maintained much more uniform, thus preventing over-treatment of body tissue at or close to the outer wall 36 of the instrument. That is to say, to obtain the same end point absorbed dose at 2 cm, it would be necessary to increase the source activity relative to that used for a completely filled (to surface 36) configuration, assuming the same radionuclide is used in both configurations.

With no limitation intended, the distensible polymeric chambers may comprise a biocompatible, radiation resistant polymer, such as Silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, PVC, C-Flex. The radioactive fluid contained within the inner chamber 32 can be made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel.

In the embodiments heretofore described, the material containing the radionuclide(s) is located in the inner chamber. The invention also contemplates that the outer chamber 34 may contain the material having the radionuclide therein while the inner chamber 30 contains the radiation absorptive material. This configuration is advantageous where a profile exhibiting higher intensity at a tissue surface with lesser penetration is desired. By using this approach, less volume of radioactive material is required than if the entire volume of the device were filled with radioactive material. Moreover, the outer chamber wall need not be spherical, yet a uniform profile is obtainable. Experiments have shown that a steeper radial absorbed source gradient can be obtained using a radiation attenuation fluid in the inner chamber 30 than otherwise obtains when only a single distensible chamber is used, as in the aforereferenced Williams U.S. Pat. No. 5,429,582. The invention also contemplates that the radioactive material in the inner core can be replaced by a core containing solid radionuclide-containing

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particles. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used in place of the fluid. This radioactive source can either be preloaded into the catheter at the time of manufacture or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. Such a solid radioactive core configuration offers the advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources.

In either the concentric spherical embodiment of FIG. 1 or the non-spherical configuration of FIG. 3, the spacing between the inner and outer chambers needs to be held somewhat constant to avoid “hot spots”. This result can be achieved by careful placement of precision blown polymer parisons or by using compressible foams or mechanical spacers in the form of webs joining the inner wall 32 to the outer wall 36.

This invention has been described herein in considerable detail in order to comply with the patent statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use such specialized components as are required. However, it is to be understood that the invention can be carried out by specifically different equipment and devices, and that various modifications, both as to the equipment and operating procedures, can be accomplished without departing from the scope of the invention itself.

What is claimed is:

1. Apparatus for delivering radioactive emissions to a body location with a uniform radiation profile, comprising:

- (a) a catheter body member having a proximal end and distal end;
- (b) an inner spatial volume disposed proximate the distal end of the catheter body member;
- (c) an outer, closed, inflatable, chamber defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall;
- (d) a material containing a radionuclide(s) disposed in one of the inner spatial volume and outer chamber; and
- (e) means disposed in the other of the inner spatial volume and outer chamber for rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber containing the radionuclides.

2. The apparatus as in claim 1 wherein said inner spatial volume is an inner closed, chamber defined by a further radiation transparent wall.

3. The apparatus of claim 1 wherein the means for rendering uniform the absorbed dose profile is a radiation attenuating material.

4. The apparatus of claim 3 wherein the radiation attenuating material is selected from a group consisting of barium sulphate, water, and X-ray contrast media.

5. The apparatus as in claim 2 wherein the radionuclide is in a fluid form.

6. The apparatus as in claim 5 wherein the fluid comprises an isotope of iodine.

7. The apparatus as in claim 1 wherein the radionuclide is a slurry of a fluid containing particles of a solid isotope.

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8. The apparatus as in claim **2** wherein the inner chamber contains the radioactive material.

9. The apparatus as in claim **1** wherein the outer chamber contains the radioactive material.

10. The apparatus as in claim **8** wherein the radioactive material is a fluid. ⁵

11. The apparatus as in claim **8** wherein the radioactive material is a solid.

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12. The apparatus as in claim **1** wherein the material containing a radionuclide comprises a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile.

13. The apparatus as in claim **2** wherein the inner and outer chambers are spherical in shape and are concentric.

* * * * *

EXHIBIT B

(12) **United States Patent**
Winkler et al.

(10) **Patent No.:** **US 6,413,204 B1**
(45) **Date of Patent:** ***Jul. 2, 2002**

(54) **INTERSTITIAL BRACHYTHERAPY APPARATUS AND METHOD FOR TREATMENT OF PROLIFERATIVE TISSUE DISEASES**

(75) Inventors: **Rance A. Winkler**, Atlanta; **Timothy J. Patrick**; **James Stubbs**, both of Alpharetta, all of GA (US)

(73) Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/293,524**

(22) Filed: **Apr. 15, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/900,021, filed on Jul. 4, 1997, now Pat. No. 5,913,813.

(51) Int. Cl.⁷ **A61N 5/00**

(52) U.S. Cl. **600/3**

(58) Field of Search **600/1-8**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,324,847 A	6/1967	Zoumboulis	128/1.2
3,872,856 A	3/1975	Clayton	128/1.2
4,417,576 A	11/1983	Baran	128/207.15
4,706,652 A	11/1987	Horowitz	128/1.2
4,754,745 A	7/1988	Horowitz	128/1.2
4,763,642 A	8/1988	Horowitz	128/1.2

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP 0340881 11/1989 A61N/5/10

EP	0867200	9/1998	
GB	2105201	3/1983 A61N/1/06
WO	9210932	7/1992 A61N/5/02
WO	9309724	5/1993 A61B/17/36
WO	9719723	6/1997 A61N/5/00
WO	9812979	4/1998 A61B/19/00
WO	9911325	3/1999	
WO	9933515	7/1999	
WO	9942163	9/1999	

OTHER PUBLICATIONS

A. Bex et al., *A System for Focal Intracavitary Irradiation of Bladder Cancer with Remote Iridium-192 Afterloading*, 21 Eur Urol 1992, 245-249 (1992).

Ashpole, R.D. et al., "A New Technique of Brachtherapy for Malignant Gliomas with Caesium-137: A New Method Utilizing a Remote Afterloading System," *Clinical Oncology*, vol. 2, 333-7 (1990).

Chun, M. et al., "Interstitial Iridium-192 Implantation for Malignant Brain Tumours. Part II: Clinical Experience," *The British Journal of Radiology*, vol. 62, 158-62 (1989).

Garfield, J. et al., "Postoperative Intracavitary Chemotherapy of Malignant Gliomas," *J. Neurosurg.*, vol. 39, 315-22 (Sep. 1973).

(List continued on next page.)

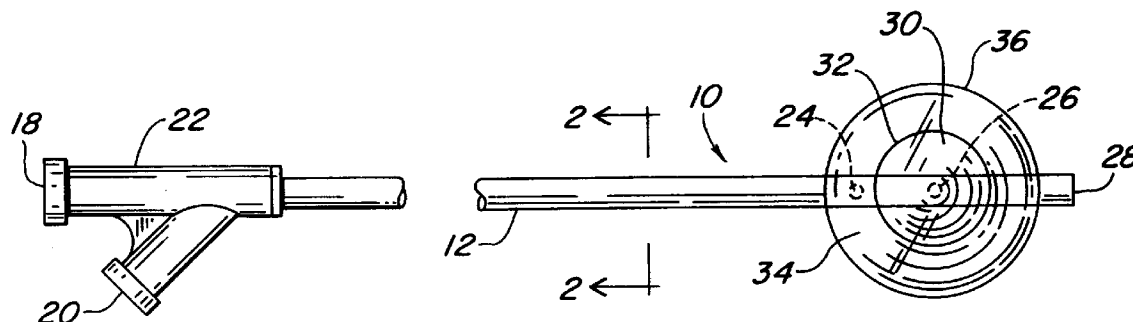
Primary Examiner—John P. Lacyk

(74) *Attorney, Agent, or Firm*—Thomas J. Engellenner; Ronald E. Cahill; Nutter, McClennen & Fish, LLP

(57) **ABSTRACT**

An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume.

36 Claims, 3 Drawing Sheets



U.S. PATENT DOCUMENTS

4,821,725	A	4/1989	Azam et al.	128/420	A
4,867,741	A	9/1989	Portnoy	604/10	
5,084,001	A	1/1992	Van't Hooft et al.	600/3	
5,084,015	A	1/1992	Moriuchi	604/96	
5,106,360	A	4/1992	Ishiwara et al.	600/2	
5,112,303	A	5/1992	Pudenz et al.	604/49	
5,152,747	A	10/1992	Olivier	604/93	
5,236,410	A	8/1993	Granov et al.	600/12	
5,429,582	A	7/1995	Williams	600/2	
5,484,384	A	1/1996	Fearnott	600/3	
5,503,613	A	4/1996	Weinberger	600/3	
5,566,221	A	10/1996	Smith et al.	378/145	
5,611,767	A	3/1997	Williams	600/2	
5,662,580	A	9/1997	Bradshaw et al.	600/3	
5,707,332	A	1/1998	Weinberger	600/3	
5,713,828	A	2/1998	Coniglione	600/7	
5,720,717	A	2/1998	D'Andrea	604/21	
5,764,723	A	6/1998	Weinberger et al.	378/65	
5,782,742	A	7/1998	Crocker et al.	600/3	
5,785,688	A	7/1998	Joshi et al.	604/141	
5,913,813	A *	6/1999	Williams et al.	600/3	
5,924,973	A *	7/1999	Wenberger	600/3	
6,036,631	A	3/2000	McGrath et al.	600/3	

6,059,812 A * 5/2000 Clerc et al. 600/3

OTHER PUBLICATIONS

Gutin, P. et al., "Brachytherapy of Recurrent Malignant Brain Tumors With Removable High-Activity Iodine-125 Sources," *J. Neurosurg.*, vol. 60, 61-8 (1984).

Johannesen, T.B. et al., "Intracavity Fractionated Balloon Brachytherapy in Glioblastoma," *Acta Neurochir (Wien)*, vol. 141, 127-33 (1999).

Leibel, S. et al., "The Integration of Interstitial Implantation Into the Preliminary Management of Patients With Malignant Gliomas: Results of a Phase II Northern California Oncology Group Trial," *Am. J. Clin. Oncol. (CCT)*, vol. 10, No. 2, p. 106 (1987).*

Roberts, D. et al., "Interstitial Hyperthermia and Iridium Brachytherapy in Treatment of Malignant Glioma," *J. Neurosurg.*, vol. 64, 581-7 (1986).*

Wu, A. et al., "Interstitial Iridium-192 Implantation for Malignant Brain Tumours, Part 1: Techniques of Dosimetry Planning," *The British Journal of Radiology*, vol. 62, 154-7 (1989).*

* cited by examiner

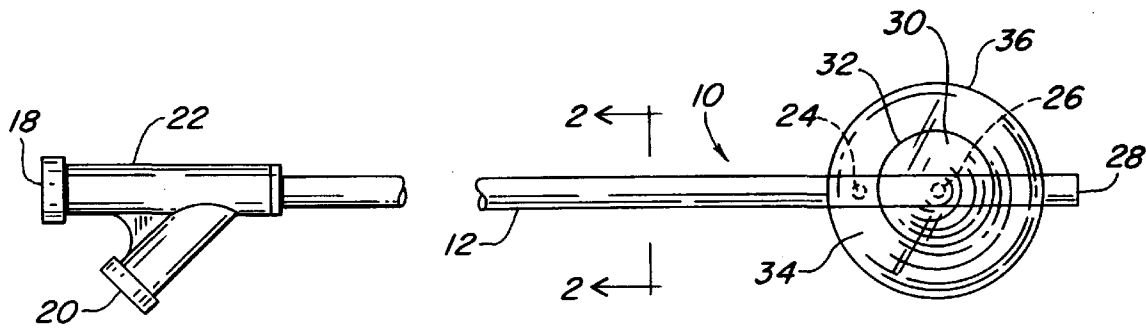


FIG. 1

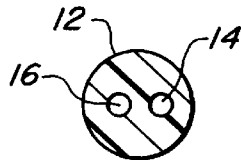


FIG. 2

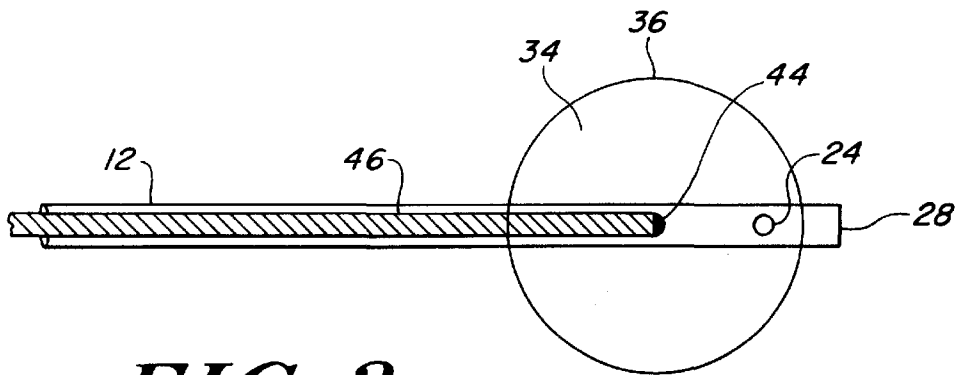


FIG. 3

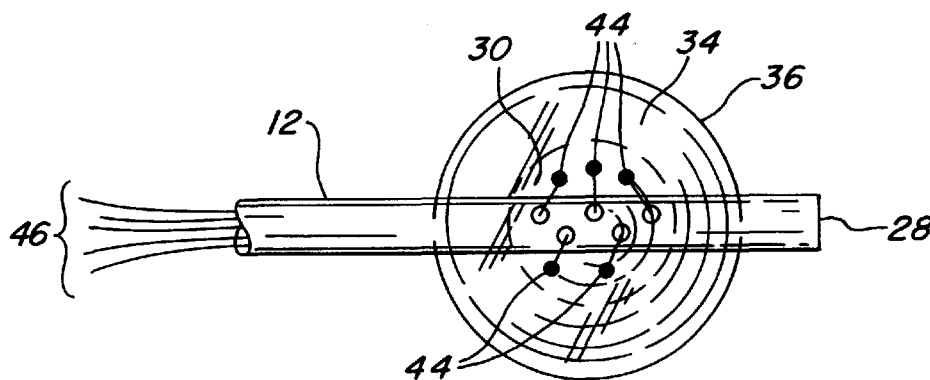


FIG. 4

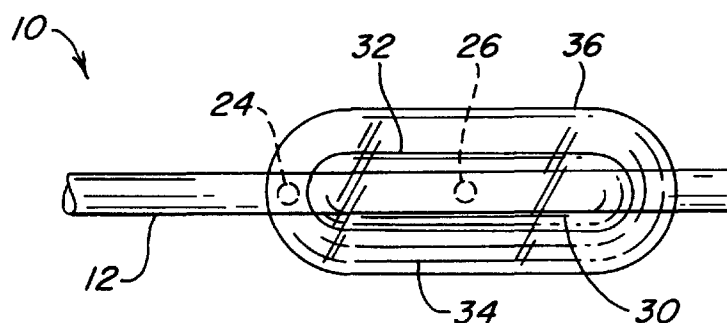


FIG. 5

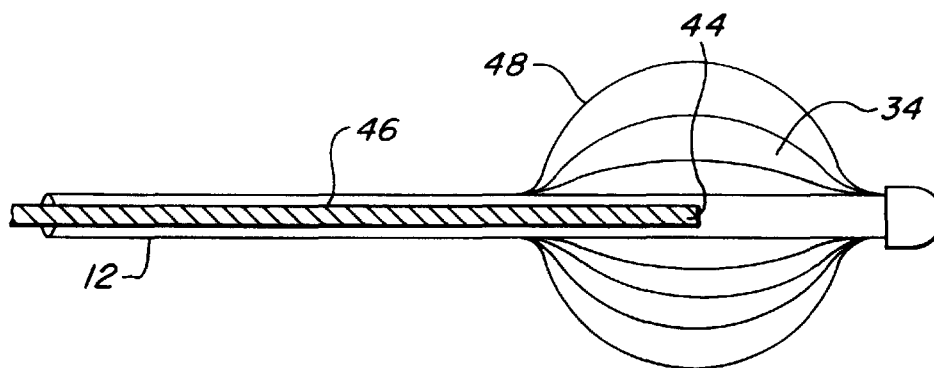


FIG. 6

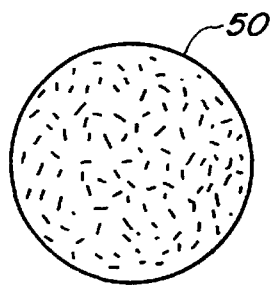


FIG. 7A

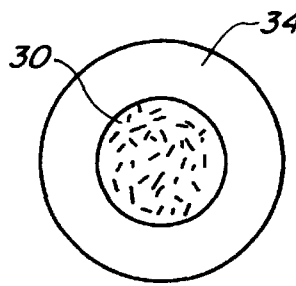


FIG. 7B

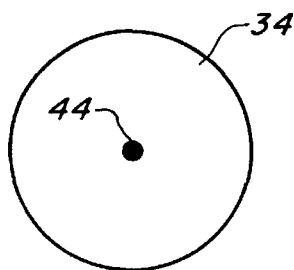


FIG. 7C

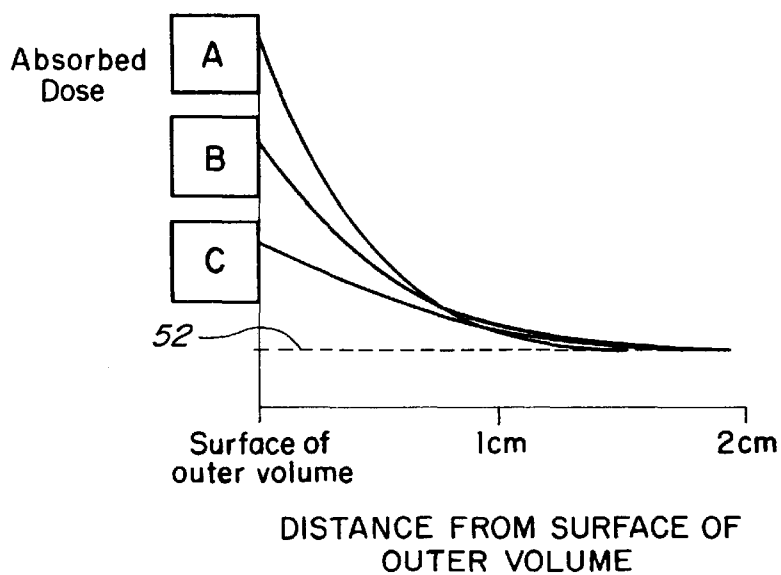


FIG. 7D

1

**INTERSTITIAL BRACHYTHERAPY
APPARATUS AND METHOD FOR
TREATMENT OF PROLIFERATIVE TISSUE
DISEASES**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation-in-part of U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997, now U.S. Pat. No. 5,913,813 the contents of which are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance or normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ¹²⁵I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a

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distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. As a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall.

There is still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location. The apparatus includes a catheter body member having a proximal end and distal end, an inner spatial volume disposed proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume, and a radiation source disposed in the inner spatial volume. The inner and outer spatial volumes are configured to provide an absorbed dose within a predetermined range throughout a target tissue. The target tissue is located between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface. The predetermined dose range is defined as being between a minimum prescribed absorbed dose for delivering therapeutic effects to tissue that may include cancer cells, and a maximum prescribed absorbed dose above which healthy tissue necrosis may result.

In different embodiments, the inner spatial volume can be defined by a distensible polymeric wall containing radioactive source material which can be a fluid material, by a solid radioactive source, or by a region containing a plurality of solid radioactive sources. The outer spatial volume is defined by an expandable surface element that may be, for example, an inflatable polymeric wall or an expandable cage. The expandable surface element can cause tissue to conform to its intended shape, and preferably, the apparatus creates absorbed isodose profiles in the target tissue that are substantially similar in shape to the expandable surface element in substantially three dimensions.

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The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. 1 is a side view of an interstitial brachytherapy apparatus of the invention for delivering radioactive emissions to body tissue;

FIG. 2 is a cross-sectional view taken along the line 2—2 in FIG. 1;

FIG. 3 is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a solid radiation source;

FIG. 4 is an additional embodiment of an interstitial brachytherapy apparatus of the invention having a radiation source comprising a plurality of solid radiation particles;

FIG. 5 depicts a further embodiment of the invention wherein the inner and outer spatial volumes of the interstitial brachytherapy apparatus are non-spherical;

FIG. 6 illustrates an interstitial brachytherapy apparatus of the invention having an expandable outer spatial volume surface; and

FIGS. 7A–D illustrate the absorbed dose versus distance into target tissue for several interstitial brachytherapy apparatus configurations.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument 10 for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. 1. Surgical instrument 10 includes a tubular body member 12 having first and second lumens 14 and 16 (FIG. 2) extending from proximal ports 18 and 20 in a molded plastic hub 22 to inflation ports 24 and 26 formed through the side wall of the tube 12 and intersecting with the lumens 14 and 16, respectively.

Affixed to the tubular body 12 proximate the distal end 28 thereof is an inner spatial volume 30 which may be defined by a generally spherical polymeric film wall 32. The interior of the inner volume 30 is in fluid communication with the inflation port 26. Surrounding inner spatial volume 30 is an outer spatial volume 34 defined by an outer polymeric film wall 36 that is appropriately spaced from the wall 32 of the inner spatial volume 30 when the two volumes are inflated or otherwise supported. Outer volume 34 encompasses inflation port 24. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radia-

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tion resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC.

The embodiment of FIG. 1 includes inner and outer spatial volumes 30 and 34, one inside the other. The outer spatial volume 34, being the volume defined by the space between the inner spherical wall 32 and the outer spherical wall 36, may be filled with air or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. The inner volume 30 is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner chamber 32 can be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is Iotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(¹²⁵I)iodo-4-hydroxybenzenesulfonate (¹²⁵I-HBS), available from Proxima Therapeutics, Inc. of Alpharetta, Ga.

As an alternative method of providing radioactive source material, such material may be coated on, chemically bonded to, or copolymerized with the material forming inner spherical wall 32.

Where the radioactive source material is provided as a fluid or gel within inner spherical wall 32, it may be desirable to provide a solid outer spherical wall 36. Should inner spherical wall 32 rupture, the radioactive source material will be retained within outer spherical wall 36 and will not leak into the patient. For further safety, the burst strength of inner spherical wall 32 may be designed so as to be lower than that of outer spherical wall 36. In this way, inner spherical wall 32 will rupture under stress first, releasing its contents into the larger combined space of the inner and outer volumes 30, 34 and releasing any pressure built up within the inner spherical wall 32 and reducing the risk that radioactive material will spill into the patient. In the event of such a rupture, radioactive fluid could be drained from the apparatus through port 24 by way of lumen 14, and also from port 26 by way of lumen 16.

In a further embodiment, illustrated in FIG. 3, instead of having the inner spatial volume 30 defined by a generally spherical polymeric film wall as at 32, the catheter body member 12 may have a solid spherical radiation emitting material 44 as the inner spatial volume 30. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used. This radioactive source can either be preloaded into the catheter at the time of manufacture or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. The solid radiation emitting material 44 can be inserted through catheter 12 on a wire 46, for example, using an afterloader (not shown). Such a solid radioactive core configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. In this embodiment solid spherical inner spatial volume 30 is surrounded by outer spherical wall 36, defining outer spatial volume 34 between the outer spherical wall 36 and the inner spatial volume 30 with the outer spatial volume 34 occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

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In a further embodiment, illustrated in FIG. 4, inner spatial volume 30, instead of comprising a single solid sphere, may comprise a plurality of radiation emitting particles 44 strategically placed within the inner spatial volume 30 so as to radiate in all directions with a substantially equal intensity. This plurality of radiation emitting particles 44 can be mounted on the distal ends of a plurality of wires 46 that are routed through the catheter body 12 and exit a plurality of ports formed through the wall of the catheter body and reaching the lumen. This arrangement allows the exact positioning of the individual radiation sources 44 to be positioned so as to generate a desired resultant profile.

As illustrated in FIG. 5, it is not essential to the invention that the volumes 30 and 34 have spherical walls, so long as the resultant dosing profile is consistent with the shape of the outer volume 34. That is, the absorbed dose within the target tissue at points equidistant from the surface 36 of the outer spatial volume 34 should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume 34. Where the inner and outer spatial volumes are created by inflatable membranes and one of the volumes contains a fluid radiation source, this can be achieved by ensuring that the spacing between the wall of the inner volume and the wall of the outer volume remain generally constant. In either the concentric spherical embodiment of FIG. 1 or the non-spherical configuration of FIG. 5, this result can be achieved by careful placement of precision blown or molded polymer partitions or by using compressible foams or mechanical spacers in the form of webs joining the inner wall 32 to the outer wall 36. The desired isodose profiles conforming to the shape of the outer spatial volume 34 can also be obtained, for example, by strategic placement of a plurality of radioactive particle sources within the inner spatial volume 30. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface 36 of the outer spatial volume 34 to be sufficiently firm so as to force the target tissue to take on the shape of the surface 36 so that the desired relationship between the isodose profiles and the target tissue is achieved.

When used in an interstitial application, the surface of the outer spatial volume 34 must establish a relationship between the inner spatial volume 30 and the target tissue so as to achieve the aforementioned isodose profile, however, the surface of the outer volume need not be a solid material. For example, as illustrated in FIG. 6, the surface of the outer volume 34 could be an expandable cage 48 formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, then be contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume 34 generally will correspond approximately to the amount of tissue resected, or be slightly larger, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 4 centimeters. In these same applications, where the radiation source is provided as a fluid within an inner balloon, the inner balloon generally has a diameter of approximately 0.5 to 3 centimeters.

FIGS. 7A–D illustrate the ability of an interstitial brachytherapy apparatus of the invention to deliver a minimum

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prescribed dose within target tissue while avoiding necrosis inducing radiation “hot spots” in tissue proximate to the apparatus. FIG. 7A illustrates an interstitial brachytherapy apparatus (device A) such as those employed in U.S. Pat. No. 5,429,582, having a single spatial volume 50 filled with a radioactive material in solution. FIG. 7B illustrates an interstitial brachytherapy apparatus (device B) of the invention having a first, inner spatial volume 30 filled with a radioactive material in solution and defined by membrane 32, and a second, outer spatial volume 34 defined by membrane 36 that is substantially evenly spaced apart from membrane 32 in substantially three dimensions. FIG. 7C illustrates an additional interstitial brachytherapy apparatus (device C) of the invention having a solid, spherical radiation source 44 as the inner spatial volume and a spherical outer spatial volume 34 defined by membrane 36.

Each of the devices illustrated in FIGS. 7A–C can be configured to deliver a substantially uniform dose at a given distance into the target tissue from the surface of the outer spatial volume 34 (or from single spatial volume 50 for device A) and to deliver a minimum prescribed dose within a given prescribed depth range into the tissue from the surface of the outer spatial volume 34. However, the different devices provide very different dose profiles as a function of distance from the surface of the outer volume as illustrated in FIG. 7D. FIG. 7D plots the absorbed dose at a given distance into the target tissue from the surface of the outer spatial volume 34 for each of the devices A, B, and C.

Each device can deliver a minimum prescribed dose 52 at a given distance from the surface of the outer spatial volume. For example, device A can readily be configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In order to reach the minimum prescribed dosage at this distance, however, device A must provide a dose proximate to the surface of the outer spatial volume that is substantially larger than the minimum prescribed dose. For the 4.0 cm diameter outer spatial volume example, the absorbed dosage would be approximately 131 Gray at the outer spatial volume surface. Ideally, radiation therapy should make use of the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue.

Comparing the plots A, B, and C, the absorbed dose profile in the space between the 2 cm site and the surface of the outer spatial volume for the devices of the invention is maintained in a much narrower range, preventing over-treatment of body tissue at or close to the surface of the outer volume of the device. Because devices B and C provide an outer spatial volume 34 between the radioactive source and

the target tissue, these devices can use hotter radiation sources to reach the minimum prescribed dosage, but take advantage of the distance between the radioactive source and the target tissue provided by the outer spatial volume 34 to reduce or eliminate hot spots in the target tissue.

Returning to the 4.0 cm diameter outer spatial volume example, if the radiation source is contained within an inner spatial volume, say a solid radioactive sphere such as device C, the absorbed dose profile becomes much different. If the radiation source is configured to provide the same 60 Gray dose at 0.5 cm into the target tissue, the absorbed dose at the outer spatial volume surface is only 94 Gray—a significant decrease from the 131 Gray dose for a type A device. In addition, the treatment range for the type C device will be extended under these circumstance as compared to the type A device, delivering a 40 Gray dose beyond 1.0 cm into the target tissue and delivering approximately double the dose at 3.0 cm into the target tissue. In one embodiment, the inner and outer spatial volumes are configured to control the absorbed dose at the outer spatial volume surface so that the absorbed dose is no greater than about 100 Gray while providing a therapeutic absorbed dose into the target tissue at the desired range. The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy. Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed “boost” of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intra-operatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is

delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

- (a) a catheter body member having a proximal end and distal end;
- (b) an inner spatial volume disposed proximate to the distal end of the catheter body member;
- (c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and
- (d) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element.

2. The apparatus of claim 1, wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

3. The apparatus of claim 2, wherein a predetermined spacing is provided between said inner spatial volume and the expandable surface element.

4. The apparatus of claim 3, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform to the tissue to the desired shape of the expandable surface element.

5. The apparatus of claim 2, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

6. The apparatus of claim 5, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

7. The apparatus of claim 5, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

8. The apparatus of claim 2, wherein the outer spatial volume has a diameter between about two and four centimeters.

9. The apparatus of claim 2, wherein the inner spatial volume is an inner closed, distensible chamber defined by a further radiation transparent wall.

10. The apparatus of claim 9, wherein the radioactive source is in a fluid form.

11. The apparatus of claim 10, wherein the expandable surface element is a solid distensible surface and the outer spatial volume is a closed, distensible chamber and the expandable surface element is a radiation transparent wall.

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12. The apparatus of claim 11, wherein a burst strength of the distensible chamber defining the outer spatial volume is greater than a burst strength of the chamber defining the inner spatial volume.

13. The apparatus of claim 1, wherein the expandable surface element is an expandable cage.

14. The apparatus of claim 13, wherein the expandable cage comprises a shape memory material.

15. The apparatus of claim 14, wherein the expandable cage comprises nitinol.

16. The apparatus of claim 1, wherein the radiation source is a solid radiation source.

17. The apparatus of claim 1, wherein the radiation source is a plurality of solid radiation sources arranged to provide an isodose profile having a shape substantially similar to the shape of the outer spatial volume.

18. The apparatus of claim 2, wherein the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions.

19. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

- (a) surgically creating access to the proliferating tissue in a patient;
- (b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;
- (c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:
 - (i) a catheter body member having a proximal end and distal end;
 - (ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;
 - (iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and
 - (iv) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element;
- (d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity until a prescribed absorbed dose has been delivered to tissue surrounding the apparatus; and
- (e) removing the interstitial brachytherapy apparatus.

20. The method of claim 19, further including placing the radioactive source into the interstitial brachytherapy apparatus after the step of placing the apparatus into the tumor resection cavity.

21. The method of claim 19, further including removing the radioactive source from the interstitial brachytherapy apparatus before the step of removing the apparatus.

22. The method of claim 19, wherein the proliferating tissue is a patient's brain.

23. The method of claim 19, wherein the proliferating tissue is a patient's breast.

24. The method of claim 19, further including configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

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25. The method of claim 24, further including providing a predetermined spacing between said inner spatial volume and the expandable surface element.

26. The method of claim 25, wherein the expandable surface element is adapted to contact tissue surrounding a resected cavity and adapted to conform the tissue to the desired shape of the expandable surface element.

27. The method of claim 24, wherein the minimum prescribed absorbed dose is 40 Gray at a distance of at least one centimeter from the expandable surface element.

28. The method of claim 27, wherein the dose rate in at least a portion of the target tissue is between about 0.4 and 0.6 Gray/hour.

29. The method of claim 27, wherein the maximum absorbed dose delivered to the target tissue is less than 100 Gray.

30. The method of claim 24, wherein the outer spatial volume has a diameter between about two and four centimeters.

31. The method of claim 24, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

32. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

- (a) surgically creating access to the proliferating tissue in a patient;
- (b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;
- (c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:
 - (i) a catheter body member having a proximal end and distal end;
 - (ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;
 - (iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and
 - (iv) a radiation source disposed in the inner spatial volume;
- (d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;
- (e) configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface; and
- (f) removing the interstitial brachytherapy apparatus.

33. The method of claim 32, wherein the step of configuring the inner and outer spatial volumes includes expanding the inner and outer spatial volumes.

34. A method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location comprising:

- (a) surgically creating access to the proliferating tissue in a patient;
- (b) surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue;

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(c) providing an interstitial brachytherapy apparatus for delivering radioactive emissions comprising:

(i) a catheter body member having a proximal end and distal end;

(ii) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(iii) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(iv) a radiation source disposed in the inner spatial volume;

(d) intraoperatively placing the interstitial brachytherapy apparatus into the resection cavity;

(e) adapting the expandable surface element to contact tissue surrounding the resection cavity to conform the tissue to the desired shape of the expandable surface element;

(f) delivering a prescribed absorbed dose to tissue surrounding the apparatus; and

(g) removing the interstitial brachytherapy apparatus.

35. The method of claim **34**, wherein the step of adapting the expandable surface element includes expanding the outer surface volume.

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36. An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

(a) a catheter body member having a proximal end and distal end;

(b) an inner spatial volume disposed proximate to the distal end of the catheter body member;

(c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and

(d) a radiation source disposed in the inner spatial volume;

wherein the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue, the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface, the apparatus providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface.

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EXHIBIT C

(12) **United States Patent**
Winkler et al.

(10) **Patent No.:** **US 6,482,142 B1**
(45) **Date of Patent:** **Nov. 19, 2002**

(54) **ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/293,524, filed on Apr. 15, 1999, which is a continuation-in-part of application No. 08/900,021, filed on Jul. 24, 1997, now Pat. No. 5,913,813.

(51) **Int. Cl.**⁷ **A61N 5/00**
(52) **U.S. Cl.** **600/3**
(58) **Field of Search** 600/1-8

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,706,652 A	11/1987	Horowitz	128/1.2
4,754,745 A	7/1988	Horowitz	128/1.2
5,422,926 A	6/1995	Smith et al.	378/121
5,562,594 A	10/1996	Weeks	600/3
5,724,400 A	3/1998	Swerdloff et al.	378/65
5,800,333 A	9/1998	Liprie	600/3

5,803,895 A	9/1998	Kronholz et al.	600/3
5,851,182 A	12/1998	Sahadevan	600/407
5,863,284 A	1/1999	Klein	600/3

FOREIGN PATENT DOCUMENTS

WO WO 97/19723 6/1997 A61N/5/00

OTHER PUBLICATIONS

Ravinder, Nath, Ph.D. et al., Development of an ²⁴¹Am Applicator For Intracavitary Irradiation of Gynecologic Cancers, I.J. Radiation Oncology, Biology, Physics, May 1988, vol. 14, No. 5, pp. 969-978.

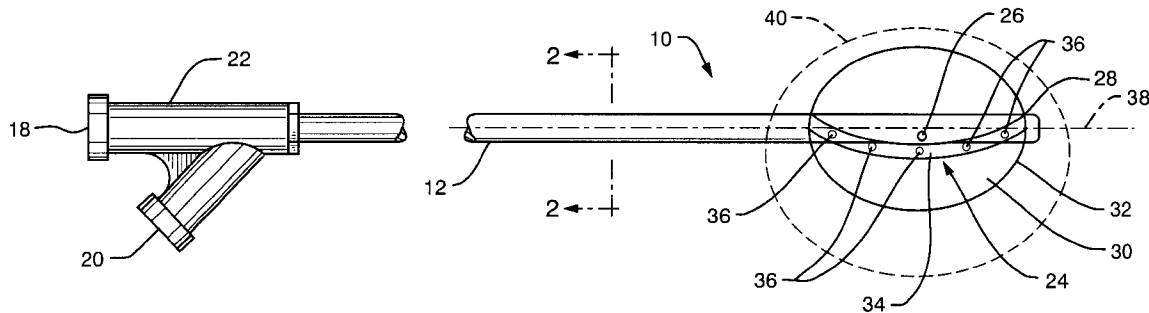
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(57) **ABSTRACT**

An interstitial brachytherapy apparatus of the invention delivers radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose curves within the target tissue. In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a longitudinal axis of the apparatus. In other configurations, asymmetric radiopaque shielding is provided between the radiation source and the target tissue. A surgical procedure using the apparatus is also described.

14 Claims, 4 Drawing Sheets





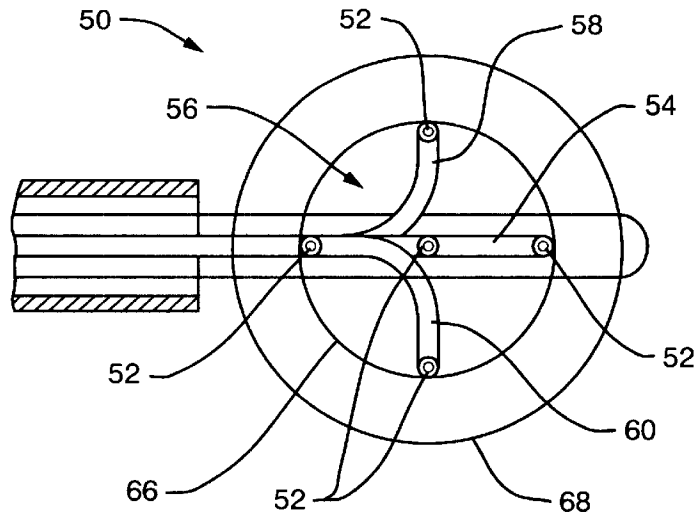


FIG. 3

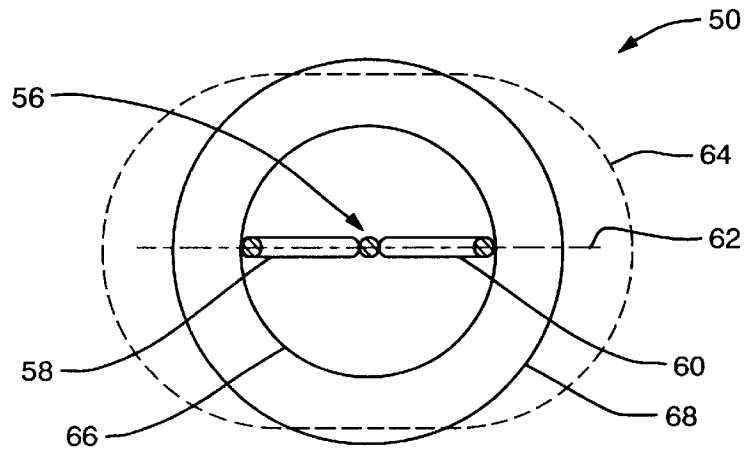


FIG. 3A

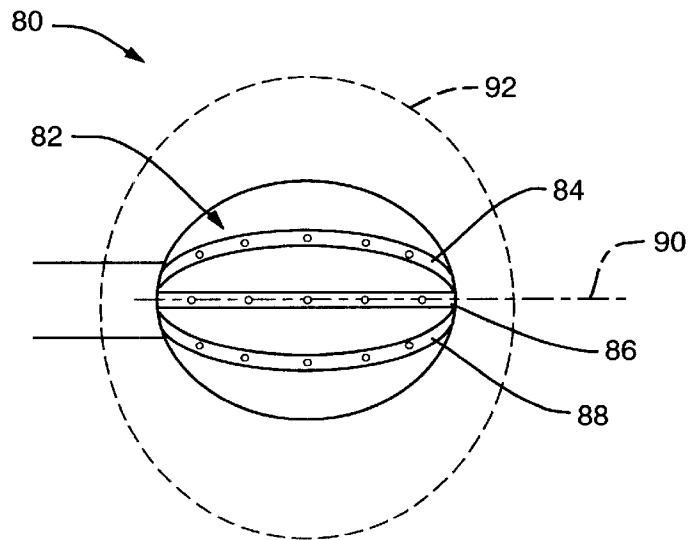


FIG. 4

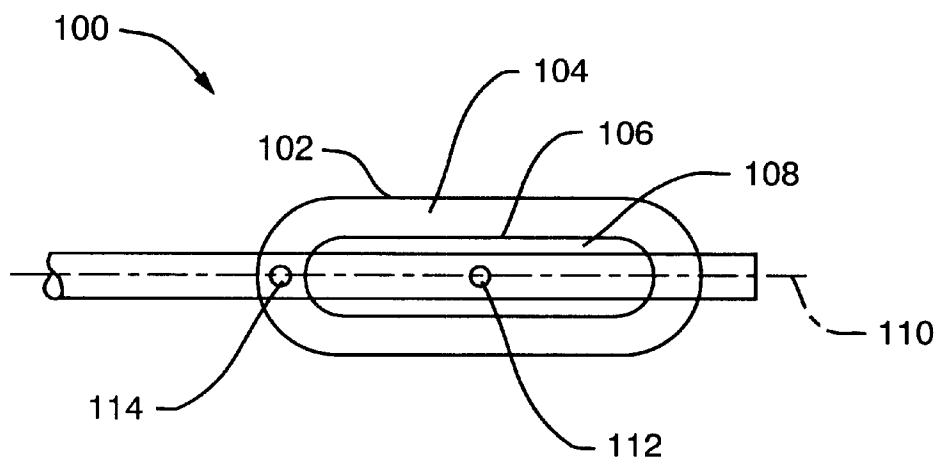


FIG. 5

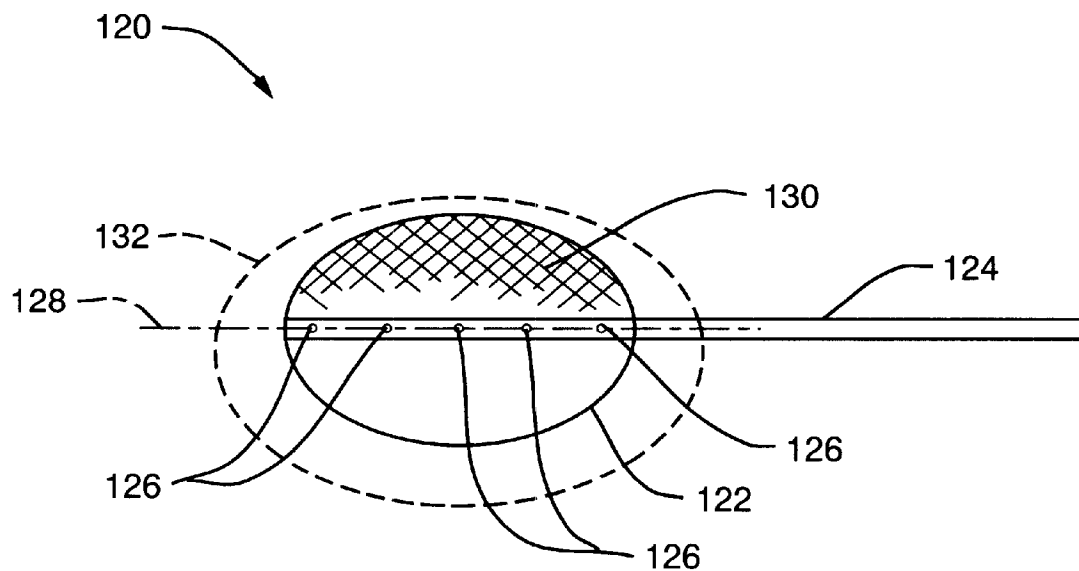


FIG. 6

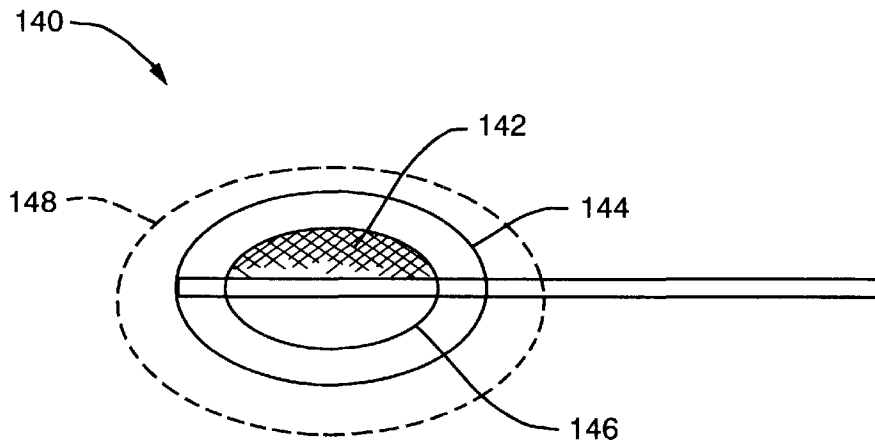


FIG. 7

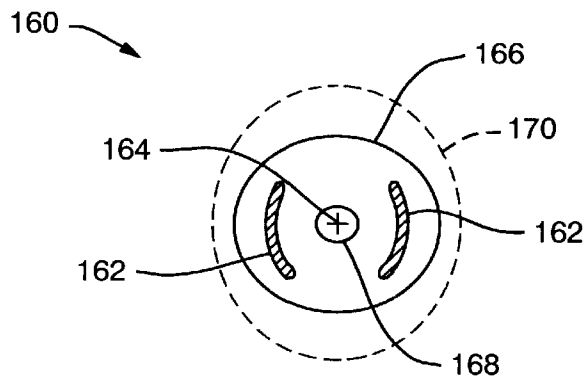


FIG. 8

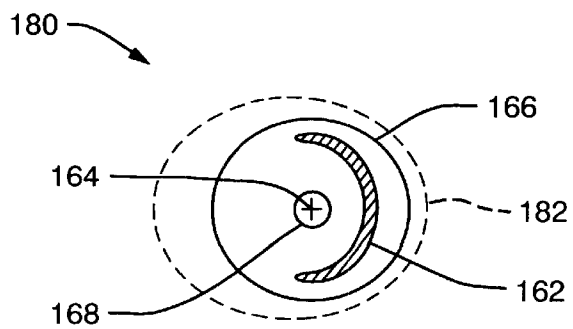


FIG. 9

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ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending U.S. patent application Ser. No. 09/293,524, filed Apr. 15, 1999, pending which is a continuation-in-part U.S. patent application Ser. No. 08/900,021, filed Jul. 24, 1997 (now issued as U.S. Pat. No. 5,913,813 to Williams et al.); the contents of these applications are specifically incorporated herein by reference.

BACKGROUND OF THE INVENTION

The invention relates generally to an apparatus for use in treating proliferative tissue disorders, and more particularly to an apparatus for the treatment of such disorders in the body by the application of radiation.

Malignant tumors are often treated by surgical resection of the tumor to remove as much of the tumor as possible. Infiltration of the tumor cells into normal tissue surrounding the tumor, however, can limit the therapeutic value of surgical resection because the infiltration can be difficult or impossible to treat surgically. Radiation therapy can be used to supplement surgical resection by targeting the residual tumor margin after resection, with the goal of reducing its size or stabilizing it. Radiation therapy can be administered through one of several methods, or a combination of methods, including external-beam radiation, stereotactic radiosurgery, and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. Owing to the proximity of the radiation source, brachytherapy offers the advantage of delivering a more localized dose to the target tissue region.

For example, brachytherapy is performed by implanting radiation sources directly into the tissue to be treated. Brachytherapy is most appropriate where 1) malignant tumor regrowth occurs locally, within 2 or 3 cm of the original boundary of the primary tumor site; 2) radiation therapy is a proven treatment for controlling the growth of the malignant tumor; and 3) there is a radiation dose-response relationship for the malignant tumor, but the dose that can be given safely with conventional external beam radiotherapy is limited by the tolerance of normal tissue. In brachytherapy, radiation doses are highest in close proximity to the radiotherapeutic source, providing a high tumor dose while sparing surrounding normal tissue. Interstitial brachytherapy is useful for treating malignant brain and breast tumors, among others.

Interstitial brachytherapy is traditionally carried out using radioactive seeds such as ¹²⁵I seeds. These seeds, however, produce inhomogeneous dose distributions. In order to achieve a minimum prescribed dosage throughout a target region of tissue, high activity seeds must be used, resulting in very high doses being delivered in some regions in proximity to the seed or seeds which can cause radionecrosis in healthy tissue. One attempt to address this problem, at least with respect to limiting dosages to critical organs near the radioactive seed site, has been to provide a shield directly on a portion of the seed or on an applicator that holds the seed to shield the particularly sensitive tissue. (E.g., Nath et al., Development of an ²⁴¹Am Applicator for Intracavitary Irradiation of Gynecologic Cancers, *Intl. J.*

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Radiation Oncology Biol. Phys., Vol., 14, pp. 969-978.) While this approach may be appropriate for some applications, it may still be overly "hot" for treating proximate tissue on the unshielded side of the seed, while not providing an effective dose on the shielded side of the seed.

Williams U.S. Pat. No. 5,429,582, entitled "Tumor Treatment," describes a method and apparatus for treating tissue surrounding a surgically excised tumor with radioactive emissions to kill any cancer cells that may be present in the tissue surrounding the excised tumor. In order to implement the radioactive emissions, Williams provides a catheter having an inflatable balloon at its distal end that defines a distensible reservoir. Following surgical removal of a tumor, the surgeon introduces the balloon catheter into the surgically created pocket left following removal of the tumor. The balloon is then inflated by injecting a fluid having one or more radionuclides into the distensible reservoir via a lumen in the catheter.

The apparatus described in Williams solves some of the problems found when using radioactive seeds for interstitial brachytherapy, but leaves some problems unresolved. The absorbed dose rate at a target point exterior to a radioactive source is inversely proportional to the square of the distance between the radiation source and the target point. As a result, where the radioactive source has sufficient activity to deliver a prescribed dose, say 2 centimeters into the target tissue, the tissue directly adjacent the wall of the distensible reservoir, where the distance to the radioactive source is very small, may still be overly "hot" to the point where healthy tissue necrosis may result. In general, the amount of radiation desired by the physician is a certain minimum amount that is delivered to a region up to about two centimeters away from the wall of the excised tumor. It is desirable to keep the radiation that is delivered to the tissue in the target treatment region within a narrow absorbed dose range to prevent over-exposure to tissue at or near the reservoir wall, while still delivering the minimum prescribed dose at the maximum prescribed distance from the reservoir wall. It is also desirable, at least in some applications, to provide these advantages while tailoring the radiation dosage to avoid fully dosing sensitive tissue or to reduce the amount of radiation that escapes the patient's body.

There is still a need for an instrument which can be used to deliver radiation from a radioactive source to target tissue within the human body with a desired intensity and at a predetermined distance from the radiation source without over-exposure of body tissues disposed between the radiation source and the target, and with the ability to shape the radiation dose to protect sensitive tissue or to protect against radiation exposure outside of the patient's body which may affect healthcare providers or others who might come close to the patient.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing an interstitial brachytherapy apparatus for delivering radioactive emissions in an asymmetric fashion to target tissue surrounding a surgical extraction site. The apparatus includes an expandable outer surface element defining an apparatus spatial volume, a radiation source disposed within the apparatus volume, and a means for providing predetermined asymmetric isodose profile within the target tissue.

In one configuration, asymmetric isodose curves are created in the target tissue by shaping or locating the radiation source so as to be asymmetrically placed with respect to a

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longitudinal axis of the apparatus. In one example of an apparatus having this configuration, an inner volume containing a liquid radioisotope is asymmetrically placed within the apparatus volume so as to result in an isodose profile in the target tissue that is asymmetric about the longitudinal axis of the apparatus.

In another example, the radiation source comprises a plurality of spaced apart solid radioactive particles disposed within the apparatus volume and arranged to provide a predetermined asymmetric isodose curve within the target tissue. In one particular example, the plurality of spaced apart radioactive particles are provided on a single elongate member that is shaped so that some of the radioactive particles are farther from the longitudinal axis of the apparatus than others. In other particular examples, a plurality of members carrying radioactive particles are provided with at least one of the members being shaped so as to place at least one radioactive particle asymmetrically with respect to the longitudinal axis of the apparatus.

An interstitial brachytherapy apparatus of the invention may also be implemented in a device having an expandable outer surface defining an apparatus volume, a radiation source disposed within and spaced apart from the expandable outer surface, and at least one asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shielding resulting in predetermined asymmetric isodose curves within the target tissue. In one embodiment, radiopaque shielding is provided on a portion of the expandable outer surface. In another embodiment, the radiation source is encompassed within a second, inner surface within the apparatus volume, with radiopaque shielding provided on at least a portion of the inner surface. In still further embodiments, one or more radiation shields are spaced apart from the radiation source and within the apparatus volume to achieve the desired asymmetric isodose distribution within the target tissue.

The invention also provides a method for treating a proliferating tissue disease using interstitial brachytherapy at an internal body location. The method includes surgically creating access to the proliferating tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a resection cavity within body tissue. An interstitial brachytherapy apparatus for delivering radioactive emissions as described above is then provided and intra-operatively placed into the resection cavity. After a prescribed absorbed dose has been delivered to tissue surrounding the apparatus, the apparatus is removed. The radioactive source material may be placed into the interstitial brachytherapy apparatus after the apparatus is placed in the resection cavity, and may be removed before the apparatus is removed. The method has particular applications to brain and breast cancers.

DESCRIPTION OF THE DRAWINGS

The foregoing features, objects and advantages of the invention will become apparent to those skilled in the art from the following detailed description of a preferred embodiment, especially when considered in conjunction with the accompanying drawings in which:

FIG. 1 is a side view of an interstitial brachytherapy apparatus of the invention for delivering asymmetric radioactive doses to body tissue;

FIG. 2 is a cross-sectional view taken along the line 2—2 in FIG. 1;

FIG. 3 is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

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FIG. 3A is an end view of the interstitial brachytherapy apparatus of FIG. 3;

FIG. 4 is a side view of an additional embodiment of an interstitial brachytherapy apparatus of the invention;

FIG. 5 is a side view of an interstitial brachytherapy apparatus of the invention configured for use with a liquid radiation source.

FIG. 6 is a side view of an interstitial brachytherapy device of the invention employing radiopaque coatings;

FIG. 7 is a side view of an interstitial brachytherapy device of the invention employing radiopaque coating and a liquid radiation source; and

FIGS. 8 and 9 are end views of interstitial brachytherapy devices of the invention employing radiopaque shields.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A surgical instrument 10 for providing radiation treatment to proliferative tissue in a living patient is illustrated in FIG. 1. Surgical instrument 10 includes a tubular body member 12 having first and second lumens 14 and 16 (FIG. 2) extending from proximal ports 18 and 20 in a molded hub 22. The first lumen 14 carries a radioactive source 24 and second lumen 16 communicates with inflation port 26 formed through the side wall of the tube 12.

Affixed to the tubular body 12 proximate the distal end 28 thereof is an outer spatial volume 30 defined by an outer polymeric film barrier 32 that is appropriately spaced from the radioactive source 24. Outer volume 30 encompasses inflation port 26. With no limitation intended, the distensible polymeric film walls may comprise a biocompatible, radiation resistant polymer, such as silastic rubbers, polyurethanes, polyethylene, polypropylene, polyester, or PVC. The outer spatial volume 30 may be filled with air, saline or, alternatively, a radiation absorbing fluid, such as a contrast media used in angiography. Alternatively, the surface of outer volume 30 need not be a solid material. For example the surface of the outer volume 30 could be an expandable cage formed from a shape memory metal, such as nitinol, or a suitable plastic, such as an expandable polyethylene cage. Such a cage can be formed in the desired shape to conform to a particular isodose profile, contracted for delivery to the target site in vivo, then expanded to cause the tissue surrounding the surgically resected region to take the appropriate shape. The size of the outer spatial volume 30 generally will correspond approximately to the amount of tissue resected. For some applications, the size of the outer spatial volume 30 may be slightly smaller than the resected volume while for other applications, the outer spatial volume will be slightly larger than the resected volume, allowing the expandable surface of the outer spatial volume to urge tissue on the surface of the resected region into the appropriate shape to promote an even dose distribution around the outer spatial volume in the target tissue. In typical applications, the outer spatial volume has a diameter of approximately 2 to 6 centimeters.

Radiation source 24 comprises a wire 34 having one or more solid radioactive particles 36 located on the wire 34. For example, radioactive micro spheres of the type available from the 3M Company of St. Paul, Minn., may be used as the solid radioactive particles. Such a solid radioactive particle configuration offers an advantage in that it allows a wider range of radionuclides than if one is limited to liquids. Solid radionuclides that could be used with the delivery device of the present invention are currently generally available as brachytherapy radiation sources. Examples of

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radioactive materials which can be selected by a person of ordinary skills in the art for use with the present invention may be found in Tables 1 to 4 of PCT Publication WO 97/19723, which is hereby incorporated by reference.

The, radioactive source **24** can either be preloaded into the catheter at the time of manufacture, or loaded into the device after it has been implanted into the space formerly occupied by the excised tumor. If loaded after implantation, the solid radiation emitting material **36** can be inserted through lumen **14** on a wire **34**, for example using an afterloader (not shown).

Radiation source **24** has an asymmetric configuration with respect to a longitudinal axis **38** of the instrument **10**. That is, radiation source **24** is shaped so as to result in an isodose profile **40** that varies radially about the longitudinal axis **38**. More simply, the isodose profile **40** of FIG. 1 has a shorter radius from the longitudinal axis **38** on the top side of the instrument **10** as shown in FIG. 1 than on the bottom side. The asymmetrically shaped isodose curve **40** may be created by providing a plurality of solid radioactive particles **36** on a curved wire **34** in a spaced apart relationship. This configuration will result in certain of the solid radioactive particles **36** being farther from the longitudinal axis **38** of the instrument **10** than others, and will result in the illustrated asymmetric isodose profile **40**. One way to provide the illustrated radioactive source **24** configuration is to form wire **34** from a solid or tubular shape memory alloy such as nickel-titanium alloys known in the art to have such properties. Wire **34** can then be preformed to the desired shape, can be compressed into a substantially straight configuration to pass through lumen **14**, and will resume its desired shape once inside volume **30** where wire **34** will be free from steric constraints imposed inside the lumen **14**. The resulting asymmetric isodose curve **40** can be further tailored by using solid radioactive particles **36** having differing specific activities to achieve the desired dosing.

In one embodiment, volume **30** and barrier **32** act to separate target tissue from the radiation source **24**. Ideally, radiation therapy should make use of the inherent difference in radiosensitivity between the tumor and the adjacent normal tissues to destroy cancerous tissue while causing minimal disruption to surrounding normal tissues. At high doses of radiation, however, the percentage of exposed cells that survive treatment decreases with first-order kinetics in proportion to increasing radiation dose. With increasing cell death comes increasing risk of necrosis or tissue death in healthy tissue that is treated with a high dose of radiation. Accordingly, it is desirable to keep the maximum radiation dose delivered by the brachytherapy apparatus as low as possible while still delivering the desired therapeutic dose to the desired range of tissue. One method for achieving this result is to provide a "hotter" radiation source in a spaced apart relationship to the target tissue. In this way, because the intensity of the radiation emitted by a source drops with the square of the distance from the source, the effective dosage may be maintained below necrosis levels in target tissue closest to the interstitial brachytherapy apparatus while providing the required dosage to a greater depth into the target tissue. (See, e.g., U.S. Pat. No. 5,913,813 which is hereby incorporated by reference in its entirety.) The capability of the apparatus of the invention to deliver absorbed doses deeper into the target tissue than prior interstitial brachytherapy devices while controlling the dose in proximity to the apparatus to reduce or eliminate the risk of healthy tissue necrosis allows for the use of brachytherapy in a greater number of cases.

For example, it is desirable to provide an interstitial brachytherapy device configured to provide a dose in a

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therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall. In a typical embodiment, the radioactive source material ranges from approximately 150 to 450 mCi in activity and encompasses most of the target treatment area with a 0.4 to 0.6 Gray/hour isodose contour. At this treatment rate, treatment may be completed in approximately 3 to 7 days, or more commonly, in approximately 3 to 5 days.

In some applications, the desired dosing profile is consistent with the shape of the outer volume **30**. That is, the absorbed dose within the target tissue at points equidistant from the surface **32** of the outer spatial volume **30** should be substantially uniform in substantially every direction. Put another way, the three dimensional isodose profiles generated by the radiation source should be substantially similar in shape to the outer spatial volume **30**. Where the apparatus of the invention is deployed in soft tissue, it may also be important for the surface **32** of the outer spatial volume **30** to be sufficiently firm so as to force the target tissue to take on the shape of the surface **30** so that the desired relationship between the isodose profiles and the target tissue is achieved.

While the interstitial brachytherapy device **10** of FIG. 1 may employ these techniques to positive effect, this device specifically alters the isodose profile for applications where particularly sensitive tissue or other concerns result in a desire to limit the dosage on one or more sides of the device as illustrated by isodose curve **40**.

In a further embodiment of the brachytherapy device **50** of the invention, illustrated in FIG. 3, three solid radiation particles **52** are provided in a linear portion **54** of radiation source **56**, while two additional radiation particles **52** are provided on co-planar extending portions **58**, **60** of radiation source **56**. An end view of the device **50** of FIG. 3 is shown in FIG. 3A with extending portions **58**, **60** provided in a single plane **62**, and resulting in isodose profile **64**. A second inner, expandable surface **66** can also be provided within outer surface **68**; the inner surface **66** enclosing the entirety of radiation source **56**.

By providing extending portions **58**, **60** having radioactive particles in the indicated co-planar relationship, areas of reduced dosage can be created on opposed sides of the device while maintaining symmetric dosing in all other directions. Of course, the number of sources and their configuration can be changed to create a desired asymmetric dosage. For example, an additional source could be added, for example above plane **62**, to result in a symmetric isodose profile in all directions except the direction below the plane **62** which would have a lower dosage.

An additional device **80** of the invention, shown in FIG. 4, includes a radiation source **82** that is made up of three wires **84**, **86**, **88**, each having a plurality of solid radiation particles. Wire **86** is a straight wire extending along the longitudinal axis **90** of the device, while wires **84**, **88** each curve as wire **34** described above with respect to FIG. 1. Wires **84**, **88** are coplanar, resulting in an isodose profile **92** that is similar to isodose profile **64** of FIG. 3A. That is, the isodose profile will be symmetric in the plane in which the wires **84**, **88** are disposed, but will have areas of reduced dosage in directions transverse to that plane (i.e., in FIG. 4, in the directions into and out of the page). As with the device **50** of FIGS. 3 and 3A, device **80** can be configured with more or fewer wires **84**, **86**, **88**, and can be provided in configurations other than the depicted co-planar configuration in order to achieve desired asymmetric isodose profiles.

The asymmetric dosing effect achieved by the devices described above can also be achieved using a liquid radiation source. For example, device **100**, illustrated in FIG. **5**, has an outer surface **102** defining an outer volume **104** and an inner surface **106** defining an inner volume **108**. The inner surface **106** is asymmetrically shaped or located with respect to the longitudinal axis **110** of the device **100** so as to result in the desired asymmetric dosing when the inner volume **108** is filled with a radioactive fluid. The inner volume **108** is spaced apart from the outer surface **102** and can be filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material contained within the inner volume **108** can be a fluid made from any solution of radionuclide(s), e.g., a solution of Ir-192, I-125 or I-131. A radioactive fluid can also be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel. One radioactive material useful in the invention is lotrex™, a sterile single use, non-pyrogenic solution containing sodium 3-(¹²⁵I)iodo-4-hydroxybenzenesulfonate (¹²⁵I-HIBS), available from Proxima Therapeutics, Inc. of Alpharetta, Ga. The inner volume **108** may be filled with radioactive fluid through port **112**. Similarly, outer volume **104** can be filled on inflated using port **114**.

A desired asymmetric dosing profile having the dosing characteristics described above may also be created by using asymmetric shielding between the radiation source and the target tissue as illustrated in FIGS. **6** through **9**. In the device **120** of FIG. **6**, a balloon **122** is located on the distal end of catheter **124**. Radioactive particles **126** are disposed along the longitudinal axis **128** of the device. A portion of the surface, either inner or outer, of balloon **122** is coated with a radiopaque material **130** to result in asymmetric isodose curve **132**. Radiopaque materials suitable for coating onto a polymeric surface of balloon **122** include, for example, barium, tungsten, bismuth, tantalum and tin.

A further device **140** having radiopaque shielding **142** is illustrated in FIG. **7**. Device **140** includes an outer volume surface **144** and an inner volume surface **146**. Inner surface **146** may contain a liquid radiation source, or may enclose one or more solid particles as used in device **120** (FIG. **6**). In device **140**, the radiopaque material **142** is coated onto a portion of either the inner or outer side of the inner volume surface **146**, resulting in a desired asymmetric isodose profile **148**.

Additional devices **160**, **180** of the invention having radiation shielding **162** are illustrated in FIGS. **8** and **9**, respectively. In these devices **160**, **180**, one or more radiation shields **162** are provided between and spaced apart from a radiation source (not shown) located along a longitudinal axis **164** of the device and the target tissue, which will be located outside of expandable surface **166**. The radiation source can include a liquid or a solid radiation source as described above. Shields **162** can be formed from radiopaque materials including those described above with respect to the radiopaque coating and can extend longitudinally from a base on the device located within the expandable surface **166**.

As shown in FIG. **8**, device **160** has two radiation shields **162** on opposed sides of catheter **168**. This configuration results in lower radiation dosing on the two sides of the device **160** on which the shields **162** are located as shown by isodose curve **170**. Device **180** (FIG. **9**) has a single radiation shield **162** resulting in an asymmetric isodose curve **182**

as shown. A person of ordinary skill in the art will recognize that other configurations may be employed to achieve desired isodose curves.

The interstitial brachytherapy apparatus of the invention can be used in the treatment of a variety of malignant tumors, and is especially useful for in the treatment of brain and breast tumors.

Many breast cancer patients are candidates for breast conservation surgery, also known as lumpectomy, a procedure that is generally performed on early stage, smaller tumors. Breast conservation surgery is typically followed by postoperative radiation therapy. Studies report that 80% of breast cancer recurrences after conservation surgery occur near the original tumor site, strongly suggesting that a tumor bed "boost" of local radiation to administer a strong direct dose may be effective in killing any remaining cancer and preventing recurrence at the original site. The apparatus described herein can be used for either the primary or boost therapy. Numerous studies and clinical trials have established equivalence of survival for appropriate patients treated with conservation surgery plus radiation therapy compared to mastectomy.

Surgery and radiation therapy are also the standard treatments for malignant solid brain tumors. The goal of surgery is to remove as much of the tumor as possible without damaging vital brain tissue. The ability to remove the entire malignant tumor is limited by its tendency to infiltrate adjacent normal tissue. Partial removal reduces the amount of tumor to be treated by radiation therapy and, under some circumstances, helps to relieve symptoms by reducing pressure on the brain.

A method according to the invention for treating these and other malignancies begins by surgical resection of a tumor site to remove at least a portion of the cancerous tumor and create a resection cavity. Following tumor resection, but prior to closing the surgical site, the surgeon intraoperatively places an interstitial brachytherapy catheter apparatus, having an inner spatial volume and an outer spatial volume as described above but without having the radioactive source material loaded, into the tumor resection cavity. Once the patient has sufficiently recovered from the surgery, the interstitial brachytherapy catheter is loaded with a radiation source. The radioactive source dwells in the catheter until the prescribed dose of radiotherapy is delivered, typically for approximately a week or less. The radiation source is then retrieved and the catheter is removed. The radiation treatment may end upon removal of the brachytherapy apparatus, or the brachytherapy may be supplemented by further doses of radiation supplied externally.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention, including, but not limited to, combinations of elements from different embodiments found herein. All references cited herein are expressly incorporated by reference in their entirety.

What is claimed is:

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:
an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

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a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves with respect to the apparatus volume.

2. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source compris-

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ing a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume.

10. The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable outer surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

* * * * *

EXHIBIT D

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Attorneys for Defendants CYTYC CORPORATION and
CYTYC SURGICAL PRODUCTS II, INC.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

XOFT, INC.,

Plaintiff,

vs.

CYTYC CORPORATION and PROXIMA
THERAPEUTICS, INC.,

Defendants.

AND RELATED COUNTERCLAIMS.

) Case No. CV 05-05312 RMW

)

) **DEFENDANT AND COUNTERCLAIMANT**
) **CYTYC CORPORATION'S OPENING**
) **CLAIM CONSTRUCTION BRIEF (PAT.**
) **L.R. 4-5(a))**

)

)

) Tutorial and Markman Hearing

) Date: December 20, 2006

) Time: To Be Set

) Room: Courtroom 6, 4th Floor

) Judge: Hon. Ronald M. Whyte

)

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Pursuant to the Agreed Scheduling Order,¹ Defendant and Counterclaimant Cytyc Corporation (“Cytyc”) respectfully submits this Brief addressing the construction of disputed terms, phrases and clauses in the asserted claims of U.S. Patent Nos. 5,913,813 (the “‘813 patent”) and 6,413,204 (the “‘204 patent”) (attached hereto as Exhibits A and B to the Declaration of Henry C. Su, respectively). Cytyc currently asserts claims 1, 2, 3, 4, 8 and 12 of the ‘813 patent and claims 1, 2, 3, 4, 8, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 30, 32, 34, 35 and 36 of the ‘204 patent against Plaintiff Xoft, Inc. (“Xoft”).

PRELIMINARY STATEMENT

The differences in the parties’ approaches to construing the disputed terms are stark. Cytyc’s proposed constructions are straightforward, applying the plain meaning that would be apparent to one of ordinary skill in the art when the disputed terms are read in light of the specification, in accordance with the Federal Circuit’s recent *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), *cert. denied*, 126 S. Ct. 1332 (2006). In contrast, Xoft insists on improperly injecting into its proposed constructions of the disputed terms limitations that are nowhere found in the claim language and are not supported by the specification, in contravention of Federal Circuit law. Xoft also repeatedly attempts to limit the claim terms to exemplary embodiments in the specification, which is also contrary to the law. In a few instances where the patent specifically defines a claim term, Xoft refuses to acknowledge that express definition, crafting instead its own definition from whole cloth. Finally, Xoft cannot hope to establish by clear and convincing evidence that certain claims terms are indefinite. The testimony of Cytyc’s expert, Dr. Lynn J. Verhey, shows that one skilled in the art, reading the disputed terms in light of the specification, understands exactly what is being claimed. Xoft’s strained interpretations of the disputed terms and its meritless allegations of indefiniteness should thus be rejected.

¹ The Agreed Scheduling Order called for Cytyc to file its Opening Claim Construction Brief on November 6, 2006. On account of the fact that the Court was moving the date for the technology tutorial and claim construction hearing from December 6-7, 2006 to December 20, 2006, the parties filed on November 3, 2006 a joint stipulation and proposed order requesting that the Court enlarge the briefing schedule. On November 7, 2006, the Court declined to enlarge the briefing schedule (other than to set the due date for the reply brief on December 7, 2006) and held that “[h]aving at least the minimum time periods set forth in Civil L.R. 7 to consider the parties’ arguments would be particularly useful to the court in a case such as this.” In response to this order, Cytyc moved promptly to finalize and file its Opening Claim Construction Brief, which is still being submitted more than 35 days before the scheduled hearing date.

BACKGROUND

I. THE TECHNOLOGY

The patents-in-suit relate to the field of treating proliferative tissue diseases like cancer with radiation. Traditionally, a patient diagnosed with a cancerous tumor would have the tumor removed and then the region of body where the tumor was located would be exposed to an external radiation beam in an attempt to ensure that any remaining cancerous cells are destroyed. One of the major disadvantages of external beam radiation therapy is that it is difficult to target just the diseased area and avoid irradiating significant portions of healthy tissue. Accordingly, it is medically desirable to use various devices and instruments to position the radiation source as close as possible to the diseased site. This technique is known as brachytherapy. The root “brachy” comes from the Greek word for “short distance.”

The patents-in-suit are directed specifically to a type of brachytherapy known as interstitial brachytherapy, in which the radiation source is introduced in close proximity to diseased cells that are within the interstices of a body tissue. This technique requires creating some sort of path through the tissue to reach the targeted site, and it can be contrasted with brachytherapy in which the radiation source is merely inserted into a natural body cavity like the bladder (intracavitary), into a body lumen like the urethra (intraluminal), or on the surface of the body (surface brachytherapy). For example, as taught by the patents-in-suit, a radiation source is introduced through the opening and cavity created by the tumor resection so that it can treat the diseased cells within the interstices of the tissue at the margins of the tumor resection site.

According to the invention described and claimed in the patents-in-suit, the radiation source is introduced into the resection cavity using a catheter. An expandable or inflatable device, such as a cage or balloon, is used to shape the resection cavity so that the radiation dose absorbed by the diseased cells within the interstices of the tissue at the margins of the cavity is made more uniform. Three primary factors affect the amount of the absorbed dose: (1) distance of the tissue to be treated from the radiation source, (2) the presence of a radiation attenuating medium such as air or a saline solution, and (3) the use of radiation shielding.

1 The patents-in-suit use these factors, individually or in combination, to improve treatment by
2 controlling the “radial absorbed dose profile” and the “three-dimensional isodose profile.” The former
3 involves controlling the absorbed dose as a function of radial distance from the radiation source to
4 points within the targeted tissue; the latter involves conforming the shape of the targeted tissue to a
5 virtual, three-dimensional surface defined by points receiving the same radiation dose. To control the
6 radial absorbed dose profile, one may surround the radiation source with a radiation attenuating
7 medium to minimize the ratio of the absorbed dose at the wall of the tumor cavity to the dose within
8 the interstices of the target tissue. If the ratio is too high, then “hot spots” can occur at the wall of the
9 cavity, which cause healthy tissue to necrose. Controlling the three-dimensional isodose profile
10 involves shaping the resected tumor cavity and adjusting the position of the radiation source relative to
11 the cavity to create a desired, virtual isodose surface on which all points receive substantially the same
12 dose. These points will be coincident with points within the interstices of the tissue to be treated.

13 **II. THE EXPERTS**

14 Although Cytac bases its proposed constructions on the intrinsic evidence, *i.e.*, the patents’
15 claim language, specifications, and prosecution histories, Cytac also proffers the testimony of Dr.
16 Lynn J. Verhey to provide the perspective of one skilled in the relevant art. *Phillips*, 415 F.3d at 1313
17 (claims must be construed from the perspective of one skilled in the art). In this case, a person of
18 ordinary skill in the art has a background in radiation oncology physics with a focus on brachytherapy.
19 Such individuals would hold a M.S. degree in Physics or Engineering, with 3 or more years of clinical
20 medical physics experience, or a Ph.D. in Physics or Engineering with 2 or more years of clinical
21 experience. (*See* Exhibit D to the Declaration of Henry C. Su (Declaration of Lynn J. Verhey, Ph.D.
22 (“Verhey Rep.”)) at 4:6-18.)

23 Dr. Verhey is an expert in the field of radiation oncology, with decades of experience. He is
24 currently a Full Professor and Vice-Chair in the Department of Radiation Oncology at University of
25 California, San Francisco. Dr. Verhey earned a Ph.D. in Physics and, in 1975, took a position as
26 Hospital Radiation Physicist at Massachusetts General Hospital (MGH) with a concurrent continuing
27 position as Assistant Professor at the Harvard Medical School. In 1990, he became Chief of the
28 Physics Division and Associate Professor in the Department of Radiation Oncology at UCSF. He has

1 taught courses in physics, radiation, and medical physics (including radiation oncology). He has
 2 conducted research on new methods of delivering radiation to cancer patients and has published over
 3 100 technical papers in that field. Dr. Verhey is a certified Therapeutic Radiological Physicist by the
 4 American Board of Radiology and is a fellow in the American Association of Physics in Medicine and
 5 the American Society of Therapeutic Radiology and Oncology. In sum, he is a well-recognized and
 6 independent expert in methods of delivering radiation to cancer patients.

7 By contrast, Xoft's expert, Paul A. Lovoi, Ph.D., did not attach a curriculum vitae to his report
 8 and his credentials in the relevant field are not otherwise apparent. Moreover, Dr. Lovoi is not
 9 independent. He is one of the founders of Xoft and was an officer of Xoft until recently. He now
 10 consults for Xoft and has worked for the company during the last decade. His report indicates a Ph.D.
 11 in physics but does not list any specific experience in the field of radiation oncology, other than 9 years
 12 of purported experience in "medical use of sources of radiation." Xoft is Dr. Lovoi's company – he
 13 founded it, he ran it, and he has devoted a good part of his life to it. This Court should weigh his
 14 opinions accordingly.

15 APPLICABLE LAW

16 Sitting *en banc*, the Federal Circuit recently clarified its guiding principles for construction of
 17 patent claims. *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). In *Phillips*, the court
 18 emphasized the "primary importance" of the language of the claims themselves:

19 It is a "bedrock principle" of patent law that "the claims of a patent define the invention
 20 to which the patentee is entitled the right to exclude." . . . That principle has been
 21 recognized since at least 1836, when Congress first required that the specification
 22 include a portion in which the inventor "shall particularly specify and point out the part,
 23 improvement, or combination, which he claims as his own invention or discovery." . . .
 24 In the following years, the Supreme Court made clear that the claims are "of primary
 importance, in the effort to ascertain precisely what it is that is patented." . . . Because
 the patentee is required to "define precisely what his invention is," the Court explained,
 it is "unjust to the public, as well as an evasion of the law, to construe it in a manner
 different from the plain import of its terms." . . .

25 415 F.3d at 1312 (citations omitted). The Federal Circuit also reaffirmed the time-honored rule that
 26 claim terms are generally to be given their ordinary and customary meaning to those skilled in the art:

27 We have frequently stated that the words of a claim "are generally given their ordinary
 28 and customary meaning." . . . We have made clear, moreover, that the ordinary and
 customary meaning of a claim term is the meaning that the term would have to a person
 of ordinary skill in the art in question at the time of the invention, i.e., as of the effective

1 filing date of the patent application. . . . The inquiry into how a person of ordinary skill
2 in the art understands a claim term provides an objective baseline from which to begin
claim interpretation.

3 *Id.* at 1312-13 (citations omitted). Likewise, the court stressed that claims must be read in light of the
4 specification. *Id.* at 1315 (“claims must be read in view of the specification, of which they are a part.”)
5 (internal quotations omitted)). Importantly, the court held that claim terms should be given “*their*
6 *broadest reasonable construction* ‘in light of the specification as it would be interpreted by one of
7 ordinary skill in the art.’” *Id.* at 1316 (citing *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364
8 (Fed. Cir. 2004) (emphasis added)).

9 The *Phillips* court repeated the venerable warning that one must “avoid the danger of reading
10 limitations from the specification into the claim.” 415 F.3d at 1323. With that warning in mind, the
11 court described the two primary instances in which the specification can limit the meaning of claim
12 terms. *First*, the patentee can choose to recite an explicit definition for a claim term in the
13 specification. *Id.* at 1316. In that case it is said that the patentee has acted as his own lexicographer
14 and the patentee’s definition “governs.” *Id.* *Second*, the specification may limit the plain meaning of a
15 claim term when the patentee disclaims or disavows certain interpretations of the term. *Id.* In other
16 words, the specification can limit the plain meaning of claim terms when the patentee has clearly set
17 forth a limiting interpretation.

18 The prosecution history is also important to consider when construing claim terms. The
19 *Phillips* court explained:

20 [W]e have held that a court “should also consider the patent’s prosecution history, if it
21 is in evidence.” . . . The prosecution history, which we have designated as part of the
22 “intrinsic evidence,” consists of the complete record of the proceedings before the PTO
23 and includes the prior art cited during the examination of the patent. . . . Like the
specification, the prosecution history provides evidence of how the PTO and the
inventor understood the patent. . . . Furthermore, like the specification, the prosecution
history was created by the patentee in attempting to explain and obtain the patent.

24 415 F.3d at 1317 (citations omitted).

25 The *Phillips* court also noted that expert testimony (on which Xoft almost exclusively relies in
26 this case) should play a lesser role in claim construction. 415 F.3d at 1317 (“[W]hile extrinsic
27 evidence ‘can shed useful light on the relevant art,’ we have explained that it is ‘less significant than
28

the intrinsic record in determining the legally operative meaning of claim language.”) (internal quotations omitted). The court added that:

extrinsic evidence in the form of expert testimony can be useful to a court for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field. . . . However, conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court. Similarly, *a court should discount any expert testimony “that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent.”*

Id. at 1318 (emphasis added; citations omitted).

One claim limitation from the ‘813 patent uses the term “means,” which creates a presumption that the limitation is drafted in “means plus function” format pursuant to 35 U.S.C. § 112, ¶ 6. *Greenberg v. Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1584 (Fed. Cir. 1996). “Construction of a means plus function limitation requires identification of the function recited in the claim and a determination of what structures have been disclosed in the specification that correspond to the means for performing that function.” *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1032 (Fed. Cir. 2002). Structure described in the specification constitutes “corresponding structure” if the specification “clearly links or associates that structure to the function recited in the claim.” *Kahn v. General Motors Corp.*, 135 F.3d 1472, 1476 (Fed. Cir. 1998).

The Federal Circuit has held that a claim must be “definite” enough to be understood by one skilled in the art:

We have stated the standard for assessing whether a patent claim is sufficiently definite to satisfy the statutory requirement as follows: If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2.

Exxon Research & Eng’g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (citing *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)). “If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds.” *Id.* See also *Fresenius Med. Care Holdings, Inc. v. Baxter Int’l, Inc.*, No. C

03-1431 SBA, 2006 U.S. Dist. LEXIS 36788, at *51 (N.D. Cal. May 24, 2006). As the party asserting invalidity, Xoft bears the burden of proving indefiniteness. Moreover, because patents enjoy a statutory presumption of validity, Xoft's burden is heightened – it must prove its case with clear and convincing evidence. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986). A claim is not indefinite merely because it poses a difficult issue of claim construction (which is not even the case here, where construction is straightforward); if the claim can be construed at all, then it is not invalid for indefiniteness. *See, e.g., Bancorp Servs., LLC v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371 (Fed. Cir. 2004). Thus, the biased, conclusory statements of Xoft's expert alone cannot establish indefiniteness by clear and convincing evidence. *See Intel Corp. v. VIA Techs.*, 319 F.3d 1357, 1367 (Fed. Cir. 2003) (expert's conclusory statements are insufficient to provide clear and convincing evidence of indefiniteness).

CONSTRUCTION OF CLAIM TERMS²

I. TERMS IN THE '813 PATENT

The claims of the '813 patent relate to an instrument comprising a concentric arrangement of an inner spatial volume and an outer spatial volume defined by an inflatable chamber, disposed near the distal end of a catheter body. One of the volumes contains a source of radiation, while the other volume may contain a radiation absorptive material. In one preferred embodiment, shown in Figure 1 of the patent, the inner volume is defined by an enclosed chamber surrounding the catheter body and containing a radioactive source. The outer chamber, concentric with the inner volume, is then inflated with air or other radiation absorbing material so that its wall contacts the wall of the surgical cavity substantially at all points. The distance between the radiation source and the wall of the outer chamber can be made constant. This embodiment permits the controlled delivery of radiation to a layer of tissue surrounding the surgical cavity.³ By manipulating the volume and type of material in the outer

² Cytyc addresses herein only those terms about which the parties disagree and which Cytyc believes to be material to resolution of this suit. As to terms not addressed, Cytyc's position is as set forth in the parties' Joint Claim Construction Statement, which Cytyc incorporates by reference herein.

³ The tissue to be treated and the resected cavity can be thought of as an orange peel with the fruit (*i.e.*, the tumor) removed. A radiation source is placed within the space previously occupied by the fruit. The thickness of the "orange

(Continued...)

chamber, the ratio of the absorbed dose at the surface of the wall of tissue to the dose at the tissue depth where the minimum dose is prescribed to be received can be controlled so as to maximize the effectiveness of the treatment and minimize adverse side effects, namely, unwanted necrosis of healthy tissue.

The '813 patent teaches that other embodiments can be used to deliver therapeutic radiation to the layer of tissue surrounding the surgical cavity. (Col 2:64 – 4:20; FIGS. 3-5.) These other embodiments include the use of a radioactive liquid within an inner inflatable chamber, a plurality of radioactive solid particles, a slurry of a fluid containing particles of a radioactive isotope or a solid radioactive source. Alternatively, these same radiation sources can be placed in the volume of space between the inner chamber and the outer inflatable chamber. Any of these embodiments might be used as a means of delivering radiation to tissue within the wall of a surgical cavity.

A. “Inner Spatial Volume” (All Asserted Claims)

Cytec's Proposed Construction	Xoft's Proposed Construction
A region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber.	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

Xoft's attempt to limit the “inner spatial volume” to a “balloon” or a “spherical solid radionuclide” should be rejected. As an initial matter, a “balloon” is not even one of the embodiments of the “inner spatial volume” described in the specification. Rather, the specification describes, as an exemplary embodiment, that “the inner spatial volume . . . may be defined by a generally spherical polymeric film wall 32.” (Col. 2:35-36 (emphasis added).) In any event, it is improper to limit the claim language to the embodiments in the specification, as Xoft proposes. *Phillips*, 415 F.3d at 1323 (“For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments.”).

(...Continued)

peel” corresponds to the thickness of the tissue to be treated – in most procedures the “orange peel” of tissue to be treated is about 2 centimeters thick. (See, e.g., '813 patent at FIG. 4.)

More fundamentally, Xoft confuses the tangible structure that defines the inner spatial volume with the volume itself. The specification provides that the inner spatial volume 30 “may be *defined by* a generally spherical polymeric film.” The film defines the boundary of the volume but the volume is the region of space within that boundary. (Exhibit C to the Declaration of Henry C. Su (American Heritage College Dictionary (“AHC”)) at 1513.) Thus, according to the specification, the inner spatial volume is simply a region of space surrounded by an outer spatial volume. (*See* col. 1:52-55 (“a first spatial volume at the distal end of a catheter and a second spatial volume defined by a surrounding of the first spatial volume by a polymeric film wall . . .”).)

Cytc’s proposed construction fully captures the plain meaning of “inner spatial volume,” which the Federal Circuit notes is of “primary importance” in claim construction. *Phillips*, 415 F.3d at 1312. A “spatial volume” is a commonly understood English term, meaning simply “a region of space.” (AHC at 1513.) The word “inner” means that that region of space is located within something else, and the specification provides that that “something else” is another (outer) “spatial volume.” (Col. 1:52-55.) “Inner spatial volume” should therefore be construed to mean “a region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber.”

B. “Outer, Closed, Inflatable Chamber” (All Asserted Claims)

Cytc’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Inflatable balloon, i.e., deflated balloon.

Cytc believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence. There is no evidence of any intent by the inventors to impart a novel or special meaning to the term and Xoft has pointed to none. As discussed above with respect to an “inner spatial volume,” Xoft’s construction improperly attempts to limit the claim term to just a balloon. But nothing in the specification limits the outer, closed inflatable chamber to a “balloon.” Xoft’s proposed construction is not supported by the specification and is contrary to law. Cytc proposes the term be given its plain meaning: an “outer, closed, inflatable chamber.” Examples of such a chamber include an inflatable balloon or an expandable cage, and as Dr. Verhey points out, an “inflatable chamber of any type”

could satisfy this limitation. This, Xoft's proposed construction should be rejected and the plain meaning of the term adopted.

C. "Predetermined Constant Spacing" (All Asserted Claims)

Cytec's Proposed Construction	Xoft's Proposed Construction
No construction required or appropriate.	Indefinite. "Predetermined" spacing is some undefined constant spacing predetermined in some undefined manner with regard to deflated outer chamber.

Cytec addresses the construction of this term in connection with its construction of the term "a predetermined constant spacing between said inner spatial volume and the radiation transparent wall" below. Cytec believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.2d at 1314 ("Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms. . . . To begin with, the context in which a term is used in the asserted claim can be highly instructive.") (citing *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms"))).

Xoft proposes no construction of this term, arguing that it is indefinite. Contrary to Xoft's assertion, the term "predetermined constant spacing" is not indefinite and has an ordinary and customary meaning to one skilled in the art. Dr. Verhey easily understood the phrase "predetermined constant spacing" – indeed, any speaker of English can understand it – to mean that the spacing between the inner spatial volume and the wall of the outer inflatable chamber is made to be substantially constant. This spacing is "predetermined" in the sense that it is chosen in advance by one skilled in the art. (Exhibit C at 1077.) Although Xoft incorrectly suggests that the patent must describe that amount of spacing, a patent does not need to describe what one skilled in the art already knows. *See S3 Inc. v. nVidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001) ("The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. . . . To hold

otherwise would require every patent document to include a technical treatise for the unskilled reader.”) (citation omitted). One skilled in the art knows how to determine an appropriate “predetermined constant spacing.” Xoft cannot possibly show that the term is indefinite by clear and convincing evidence.

D. “Predetermined Constant Spacing Between Said Inner Spatial Volume And The Radiation Transparent Wall” (All Asserted Claims)

Cytec’s Proposed Construction	Xofter’s Proposed Construction
The spacing between the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, can be made constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical.	Indefinite. <i>See</i> “predetermined constant spacing,” <i>supra</i> , § I.C.

Xofter proposes no construction of this term, arguing only that it is indefinite. The conclusory statement of Dr. Lovoi, who works for Xofter and thus cannot provide a neutral opinion, does not come close to providing the clear and convincing evidence needed for Xofter to show indefiniteness. To the contrary, the term is readily understood by those skilled in the art. As Dr. Verhey explains, the term means that the spacing between the inner spatial volume and the radiation transparent wall of the outer, closed inflatable chamber, when inflated, can be made constant. If the outer chamber is spherical, then the distance is constant in all directions. If the outer chamber is cylindrical, then the distance is constant around a radial plane that is perpendicular to the axis of the catheter. (Verhey Rep. at 7:2-5.) This plain meaning construction should be adopted. *Phillips*, 415 F.3d at 1312 (plain meaning is of “primary importance”).

E. “Rendering Uniform” (All Asserted Claims)

Cytec’s Proposed Construction	Xofter’s Proposed Construction
No construction required or appropriate.	Making the same, i.e., causing to have the same value or characteristic at all points.

Cytec addresses the construction of this term in connection with its construction of the term “means . . . for rendering uniform the radial absorbed dose profile of the emissions” below. Cytec

believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.3d at 1314.

F. “Means . . . For Rendering Uniform The Radial Absorbed Dose Profile Of The Emissions “ (All Asserted Claims)

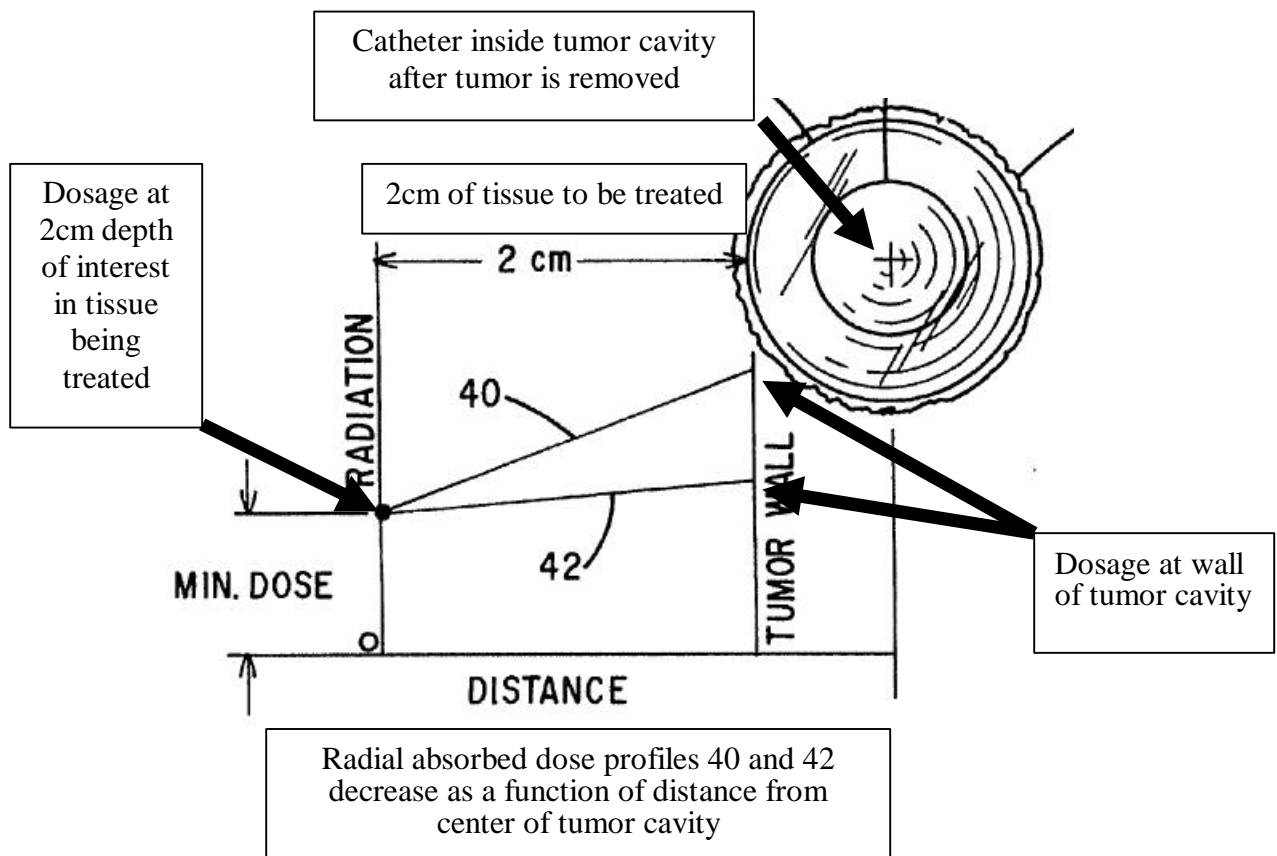
Cytec’s Proposed Construction	Xoft’s Proposed Construction
<i>Disputed Function:</i> Modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the absorbed dose at the surface of the tissue.	<i>Disputed Function:</i> Making the dose along a radius extending from the radionuclide outwardly from the outer chamber wall the same at every point on the radius.
<i>Disputed Structure:</i> A radiation absorbing or attenuating material, <i>e.g.</i> , air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfite.	<i>Disputed Structure:</i> No such means disclosed in the ‘813 patent, means for making more uniform disclosed as substance within outer chamber.

Because this is a “means-plus-function” limitation subject to 35 U.S.C. § 112, ¶ 6, the Court must construe the limitation’s function as well as the structure disclosed in the specification that corresponds to that function. *BBA Nonwovens Simpsonville, Inc. v. Superior Nonwovens, L.L.C.*, 303 F.3d 1332, 1343 (Fed. Cir. 2002) (Construction of a means-plus-function limitation “requires the court to first identify the function of the means-plus-function limitation and next identify the corresponding structure in the written description necessary to perform that function.”). The function required by this limitation is “rendering uniform the radial absorbed dose profile of the emissions.” As Dr. Verhey explains, the radial absorbed dose profile is defined as the absorbed dose in tissue, varying as a function of distance from the center of the cavity along a particular direction of interest. (Verhey Rep. at 6:21-23.) In the ‘813 patent, the direction of interest would be from the wall of the surgical cavity to a depth in the target tissue at which a prescribed therapeutic dose is defined. (*Id.*) These profiles are shown as lines 40 and 42 in the ‘813 patent at Figure 4, reproduced on the next page and annotated for discussion purposes:

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The patentees have defined in the specification what they mean by “rendering uniform the radial absorbed dose profile of the emissions.” *Phillips*, 415 F.3d at 1316 (claims must be read in light of the specification). In Figure 4, line 40 is a plot of the absorbed dose as a function of radial distance that would be obtained if there were no structure defining an inner volume, *i.e.*, if the entire spherical volume of the tumor were completely filled with radioactive fluid. (Col. 3:20-24.) Plot 42, by contrast, shows the absorbed dose as a function of radial distance when the radioactive fluid is contained within an inner volume (defined by a polymeric film wall) and is surrounded by a radiation absorbing material contained in the outer volume. (Col. 3:24-28.) According to the specification, “[c]omparing plots 40 and 42, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2cm site and the wall of the outer balloon is maintained *much more uniform*, thus preventing over-treatment of body tissue at or close to the outer wall 36 of the instrument.” (Col. 3:28-33 (emphasis added).) As Dr. Verhey explains, plot 42 in Figure 4 shows a smaller ratio of the absorbed dose at the wall of the tumor cavity to the dose at the 2cm depth of interest than plot 40. Thus, as the specification defines the term, “rendering uniform the radial

absorbed dose profile of the emissions” means modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the dose at the surface of the tissue, as exemplified by the difference between the slopes of plots 40 and 42.

Xoft’s construction of this function is unreasonable because it excludes the preferred embodiments shown in the specification. “A claim construction that excludes a preferred embodiment . . . is ‘rarely, if ever, correct.’” *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1374 (Fed. Cir. 2005) (quoting *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005)); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) (same). In the diagram in Figure 4, the radial absorbed dose profile plot 42 does not show the same dose at every point along the radius, as Xoft would require. Rather, the ratio of the dose at the cavity wall to the dose at the depth of interest is less than that for the configuration in plot 40, consistent with Cytyc’s construction.

The corresponding structure disclosed in the specification for performing this function is a radiation absorbing or attenuating material, *e.g.*, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfite. *Kahn*, 135 F.3d at 1476 (holding that structure described in the specification is corresponding structure if the specification “clearly links or associates that structure to the function recited in the claim.”). Xoft appears to agree, suggesting that the “substance within the outer chamber” corresponds to the function for making the radial absorbed dose profile more uniform.

G. “The Radioactive Material” (Claim 8)

Cytyc’s Proposed Construction	Xoft’s Proposed Construction
The material of claim 1 containing a radionuclide.	Indefinite because no antecedent.

Again, Xoft offers no construction of this term, arguing only that it is indefinite. Xoft’s argument fails. Claim 8 depends from claim 1, and it is obvious that the “the radioactive material” in claim 8 clearly refers back to “a material containing a radionuclide” described in claim 1, given that the “radionuclide” is the only radioactive material mentioned in claim 1. Anyone skilled in the art

would know that the “radioactive material” in claim 8 refers to the “material containing a radionuclide” in claim 1. Claim 8 is therefore not indefinite.

H. “A Plurality Of Radioactive Solid Particles Placed At Pre-determined Locations Within The Inner Spatial Volume To Provide A Desired Composite Radiation Profile” (Claim 12)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles.	Static array of solid radioactive particles each placed in a single location and mounted on distal ends of separate wires. “Desired composite radiation profile” is indefinite.

Xoft’s proposed construction of this term improperly imports limitations from the specification that are merely examples of the preferred embodiment. The ordinary meaning of this claim term, which Cytec proposes as the proper construction here, follows the language of the claim: “A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles.” (See AHC at 286 (defining composite as “made up of distinct components; compound”).)

II. TERMS IN THE ‘204 PATENT

The ‘204 patent, which is a continuation-in-part of the ‘813 patent, describes an apparatus for brachytherapy and a method of using it for interstitial delivery of radiation to diseased cells within the interstices of the tissue surrounding the cavity created by the surgical removal of proliferative tissue. The apparatus includes a catheter body member having a proximal end and a distal end, an inner spatial volume proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element proximate to the distal end of the body member, and surrounding and concentric with the inner spatial volume. In a preferred embodiment, a radiation source is disposed within the inner spatial volume.

The ‘204 patent describes a number of embodiments that can be used in the apparatus for delivering a therapeutic dose of radiation, including, without limitation, radioactive microspheres (FIG. 4), concentric non-spherical chambers (FIG. 5), a single solid radiation emitting material surrounded by an expandable cage defining the shape of the tumor cavity (FIG. 6), a radioactive fluid filling the

outer chamber (FIG. 7a), a radioactive fluid filling the inner chamber and the outer chamber filled with air or other radiation absorbing substance (FIG. 7b), and a single solid source surrounded by an outer chamber filled with a radiation absorbing substance (FIG. 7c). Figure 7d shows examples of radiation profiles which might be obtained by the embodiments shown in Fig. 7a-7c where the depth of interest is shown as 2cm from the surface of the outer volume. As can be seen, different embodiments can be used to vary the ratio of the dose at the prescribed depth to the dose at the wall of the cavity.

A. “Interstitial” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Site in natural or surgically created cavity in body.

Cytec addresses the construction of this term in connection with its construction of the term “interstitial brachytherapy” below. Cytec believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate. *See Phillips*, 415 F.3d at 1314.

B. “Brachytherapy” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
Radiation therapy delivered by a spatially confined radiation source at or near the site of the diseased tissue.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor or other proliferative tissue disease site.

The parties mostly agree on the definition of “brachytherapy” with two exceptions. *First*, Xoft attempts to limit brachytherapy to the use of a “radionuclide” for irradiating tissue. But radiation can be provided from sources that are not radionuclides (but that can be equivalent to radionuclides), *e.g.* an X-ray tube. (*See Exhibit F to the Declaration of Henry C. Su (The Physics of Radiation Therapy)* at 418 (“Brachytherapy is a method of treatment in which sealed radioactive sources are used to deliver radiation at a short distance by interstitial, intracavitary, or surface application.”).) There is no reason to limit brachytherapy to use of a radionuclide and Xoft’s construction should be rejected. *Second*, Xoft improperly attempts to limit brachytherapy to treatment of tumors or other proliferative tissue

diseases. But there is no basis for such a limitation, as radiation can be applied to any diseased tissue as a doctor believes appropriate.

C. “Interstitial Brachytherapy” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
Brachytherapy applied directly to the interspaces of a body tissue, where the interspaces are not naturally occurring.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor site in a natural or surgically resected cavity in a body.

Xoft has, for almost all the other disputed terms in the ‘204 patent, improperly added limitations that are not supported by the terms’ plain meaning or the patent specification or prosecution history. With respect to “interstitial brachytherapy,” which the inventors specifically defined in the prosecution history as excluding certain types of therapies, Xoft now improperly redefines the term in a manner inconsistent with the inventors’ clear statements. Xoft may not blithely ignore the intrinsic evidence.

Specifically, Xoft’s attempt to include “natural” body cavities in its definition of “interstitial brachytherapy” is directly contrary to the patent’s prosecution history. During prosecution of the ‘204 patent, in traversing a rejection from the examiner, the inventors distinguished between brachytherapy applied to a natural body cavity and interstitial brachytherapy:

Turning to the cited prior art, the Ishiwara device comprises a thermotherapeutic apparatus having a catheter body member, an inner lumen surrounded by an outer lumen, and a radiation source contained within the inner lumen. As disclosed in col. 4, lines 19-23, Ishiwara’s apparatus is inserted into a body cavity. . . . Hence the apparatus does not provide *interstitial* radiation treatment, as Applicant’s invention requires, but rather intercavitary radiation treatment.

(Exhibit E to the Declaration of Henry C. Su (12/20/00 Amendment and Response (“Amendment”)) at 11 (emphasis in original; internal citations omitted).)

Similarly, with respect to another reference, the inventors distinguished intraluminal therapy from interstitial therapy:

Weinberger discloses in Figure 17 an intercavitary radiotherapy device for insertion within a patient’s lumen. . . . Like Ishiwara, Weinberger’s apparatus does not provide *interstitial* radiation treatment, as Applicant’s invention requires, but instead *intraluminal* radiation treatment. Whereas Applicant’s device treats disease that is

embedded in tissue (e.g., breast cancer), Ishiwara and Weinberger treat disease in a luminal cavity. For this reason, in Ishiwara and Weinberger, the catheters and expandable balloons are very different than those of Applicant's invention.

(Amendment at 12 (emphasis in original; internal citations omitted).) In light of these clear statements, Cytac is surprised that Xofig would even attempt to propose a construction of "interstitial brachytherapy" that included natural body cavities or lumens.

In summary, the inventors have specifically excluded "intercavitary" or "intraluminal" radiation therapy – *i.e.*, insertion of a brachytherapy apparatus within a natural body cavity or lumen – from the definition of "interstitial brachytherapy." Cytac's proposed construction comports with the plain meaning of the claim term, based on the inventors' disclaimer in the prosecution history.

D. "Inner Spatial Volume" (All Asserted Claims)

Cytac's Proposed Construction	Xofig's Proposed Construction
A region of space surrounded by an outer spatial volume that is defined by an expandable surface element.	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

Xofig's attempt to limit the "inner spatial volume" to a "balloon" or a "spherical solid radionuclide" should be rejected. A "balloon" is not even one of the embodiments of the "inner spatial volume" described in the specification. Rather, as in the '813 patent, the specification of the '204 patent describes, as an exemplary embodiment, that "the inner spatial volume 30 . . . *may* be defined by a generally spherical polymeric film wall 32." (Col. 3:58-59.) In any event, it is improper to limit the claim language to the embodiments in the specification, as Xofig proposes. *Phillips*, 415 F.3d at 1323 (one must "avoid the danger of reading limitations from the specification into the claim.").

More fundamentally, Xofig continues to confuse the structure that defines an inner spatial volume with the volume itself. The specification provides that the inner spatial volume 30 "may be defined by a generally spherical polymeric film." The film defines the boundary of the volume but the volume is the region of space within that boundary. Thus, according to the specification, the inner spatial volume is simply a region of space surrounded by an outer spatial volume. (*See* col. 2:39-45 ("The apparatus includes . . . an inner spatial volume disposed proximate to the distal end of the catheter body member, [and] an outer spatial volume defined by an expandable surface element

disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume . . .”).)

Cytec’s proposed construction fully captures the plain meaning of “inner spatial volume,” which the Federal Circuit notes is of “primary importance” in claim construction. *Phillips*, 415 F.3d 1312. A “spatial volume” is a commonly understood English term, meaning “a region of space.” (AHC at 1513 (defining “volume” as “the amount of space occupied by a three-dimensional object or region of space, expressed in cubic units”).) The word “inner” means that that region of space is located within something else, and the specification provides that that “something else” is another (outer) “spatial volume.” (Col. 1:52-55.) Thus, “inner spatial volume” should be construed to mean “a region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber.”

E. “Outer Spatial Volume” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate. Alternatively: a region of space defined by an expandable surface element and surrounding an inner spatial volume.	Balloon or cage.

Cytec believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. Thus, “outer spatial volume” should be construed to mean “outer spatial volume.”

Xoft’s proposed construction of the term, like its proposed construction of “inner spatial volume,” confuses the outer spatial volume with the “expandable surface element” that defines its boundary. The “outer spatial volume” is a region of space that is *defined* by an “expandable surface element” but it is not the “expandable surface element” itself. (*See* col. 3:61-65.) If the Court is inclined to construe “outer spatial volume,” then the term should be construed as “a region of space defined by an expandable surface element and surrounding an inner spatial volume.” This is consistent with the ordinary meaning of the claim term in view of the specification.

F. “Expandable Surface Element” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate. Alternatively: a device that can be expanded or inflated, such as an expandable cage or an inflatable balloon.	Deflated balloon or collapsed cage.

Cytec believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. “Expandable surface element” should be construed to mean “expandable surface element.”

Xoft’s attempt to limit the term to a “deflated balloon or a collapsed cage” is improper, and there is no support for doing so in any of the intrinsic evidence. Something that is “expandable” is capable of expansion (or inflation) and can be in any state of expansion (or inflation) from no expansion to full expansion. Indeed, as Dr. Verhey explains, a person having ordinary skill in the art would expect to have to expand the expandable surface element in order to practice the invention of the ‘204 patent. (Verhey Rep. at 9:17-20, 10:16-18.) A construction that limits this element to a “deflated” or “collapsed” state is unreasonable and erroneous.

G. “Radiation Source” (All Asserted Claims)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Radionuclide

Cytec believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. A “radiation source” is simply that—a radiation source. Xoft’s attempt to limit a “radiation source” to just radionuclides, a specific kind of source, is unsupportable.

H. “Minimum Prescribed Dose” (Claims 2, 18, 24, 32, & 36)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
Minimum prescribed dose received within a target tissue for delivering therapeutic effects.	Minimum dose needed to treat cancer cells.

Xoft’s attempt to limit this term to the provision of a dose to treat cancer cells is improper and unsupported. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. The meaning can be readily discerned from the context of the surrounding claim language – “a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue.” (*See, e.g.*, col. 8:31-33.) *See also Phillips*, 415 F.3d at 1314 (“Quite apart from the written description and the prosecution history, the claims themselves provide substantial guidance as to the meaning of particular claim terms. . . . To begin with, the context in which a term is used in the asserted claim can be highly instructive.”)

I. “Delivering A Prescribed Absorbed Dose” (Claim 34)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite – the patent contains no information on how to obtain a prescribed dose, much less a prescribed dose using an expandable surface element.

Cytec believes that no construction of this term is required or appropriate. The term has its ordinary and customary meaning to one skilled in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. Contrary to Xoft’s assertion, the phrase is not indefinite because a “prescribed absorbed dose” refers to the fact that the amount of the dose to be delivered to a target tissue is within the discretion (i.e., prescription) of a person with ordinary skill in the art to determine. For example, a radiation oncologist determines, using treatment planning software or some other reference or tool, the proper dosage for each patient, depending on a number of physiological factors. The patient-specific

amount of radiation is a “prescribed dose.” As to how the dose is delivered, Dr. Verhey explains that “once the inflatable expandable surface element is in contact with the surface of the surgical cavity, the dose at the prescription depth can be delivered once the radiation source is introduced into the catheter.” (Verhey Rep. at 9:26-28 (citing col. 5:66 – 6:28).) Delivering a prescribed absorbed dose is not indefinite and the term means exactly what it says—delivering a prescribed absorbed dose.

J. “The Inner And Outer Spatial Volumes Are Configured To Provide A Minimum Prescribed Absorbed Dose” (Claim 2 & 36) And “Configuring The Inner And Outer Spatial Volumes To Provide A Minimum Prescribed Absorbed Dose” (Claims 24 & 32)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
<p>The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue;</p> <p>and</p> <p>Configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue.</p>	<p>Indefinite – configured volumes are expanded volumes, but no cause and effect relationship between configuring of inner and outer volumes and providing dose of any prescribed amount.</p>

Contrary to Xoft’s contention, this term is not indefinite. The ‘204 patent discloses in detail the various ways in which a person of ordinary skill in the art can achieve a configuration of the inner and outer spatial volumes that will deliver a minimum prescribed dose to a target tissue of interest. (See, e.g., col. 5:22-41; col. 6:16 – col. 7:28.) As Dr. Verhey explains:

[W]here the radioactive material is disposed in the inner spatial volume, the rate at which the dose falls off between the surface of the surgical cavity and the depth at which the minimum dose is to be prescribed, can be controlled by modifying the quantity and type of radiation absorbing material contained within the outer spatial volume. The safe delivery of the minimum prescribed dose at the depth of interest requires that the tissue intervening between the surface of the cavity and the depth of interest receive a dose which is equal to or greater than the prescribed dose but less than that which would necrose (i.e., lethally damage) healthy tissue.”

(Verhey Rep. at 8:25 – 9:3.) Because one skilled in the art knows how to configure the spatial volumes to provide the minimum prescribed absorbed dose, the term is not indefinite.

K. “A Minimum Distance Outward From The Outer Spatial Volume Expandable Surface” (Claims 2, 24, 32, & 36)

Cytc’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite because it is some unknown distance from deflated balloon or collapsed cage. Patent contains no information regarding determination of minimum distance.

Cytc believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

The meaning of “a minimum distance outward from the outer spatial volume expandable surface” is not indefinite and can be readily discerned from the context of the surrounding claim language – “the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface.” The disputed phrase refers to the minimum distance outward from the expandable surface element that defines the outer spatial volume. This minimum distance defines the thickness of a layer of target tissue which, in the determination of a person of ordinary skill in the art, includes the region in which diseased cells might reside. (Verhey Rep. at 9:6-9.)

L. “Controlled Dose” (Claim 2, 24, 32, & 36)

Cytc’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite because configuration, i.e., expansion, of inner and outer volumes does not control dose.

Cytc addresses the construction of this term in connection with its construction of the phrase “providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface” below. Cytc believes that a separate

construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

M. “To Reduce Or Prevent Necrosis In Healthy Tissue Proximate To The Expandable Surface” (Claims 2, 24, 32, & 36)

Cytc’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite – patent does not describe providing a dose through expandable surface – improper functional limitation in apparatus claim.

Cytc addresses the construction of this term in connection with its construction of the phrase “providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue proximate to the expandable surface” below. Cytc believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

N. “Providing A Controlled Dose At The Outer Spatial Volume Expandable Surface To Reduce Or Prevent Necrosis In Healthy Tissue” (Claims 2, 24, 32 & 36)

Cytc’s Proposed Construction	Xoft’s Proposed Construction
Controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface	Indefinite because radiation dose is not provided when outer volume surface is “expandable”, i.e., is a deflated balloon or a collapsed cage. Also indefinite because patent contains no information on how to provide dose that will reduce or prevent necrosis in healthy tissue. In context, the word “necrosis” and the term “necrosis in healthy tissue” are indefinite.

Xoft does not offer a construction of this disputed term; it only argues that the term is indefinite. But the term is well understood by those of skill in the art. Dr. Verhey explains that by adjusting the distance between the radiation source and the surface of the outer spatial volume, or by adjusting the type of radiation absorbing material in the outer spatial volume, the ratio of the dose at the surface of the outer spatial volume to the prescribed dose at the depth of prescription can be

controlled. (Verhey Rep. at 9:12-15.) The dose must not be so high that it causes necrosis to occur in healthy tissue that is in contact with the expandable surface; persons of skill in the art will know how high such a dose may be before a significant percentage of healthy cells necrose. (*Id.*)

O. “Adapting The Expandable Surface To Contact Tissue Surrounding The Resection Cavity To Conform The Tissue” (Claim 34)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite because expandable surface, i.e., deflated balloon or collapsed cage, neither contacts nor conforms the tissue surrounding the resection cavity. The patent contains no information on how this could be done.

Cytec believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term. The term “adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue to the desired shape of the expandable surface element” means adapting the expandable surface so that it comes into contact with the tissue forming the wall of the resection cavity and conforms that tissue to its shape. This comports with the ordinary meaning of the claim term.

Xoft’s indefiniteness assertion is premised on its flawed construction of “expandable surface,” which requires that the surface be in a deflated or collapsed state. The fact that claim 34, however, requires the expandable surface to contact the tissue surrounding the resection cavity establishes that Xoft’s construction of “expandable surface” is erroneous. Under a proper construction, the expandable surface can be inflated or expanded to some degree so that it contacts the tissue and conforms the tissue to its shape. Dr. Verhey explains: “the volume of the expandable surface can be adjusted by inflation until the surface of the expandable volume is in contact with the surface of the resection cavity at all points. In this state, the shape of the resection cavity conforms to the shape of the expandable surface.” (Verhey Rep. at 9:18-20 (citing col. 5:47-61).)

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P. “Desired Shape Of The Expandable Surface Element” (Claims 4, 26, & 34)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
The desired shape of the expandable surface element.	Indefinite. Patent contains no information regarding the desired shape of an expandable surface element, i.e., a deflated balloon or collapsed cage.

Cytec believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

This term is not indefinite, as Xoft wrongly contends. The desired shape of the balloon is within the discretion of those skilled in the art. According to Dr. Verhey, “the desired shape of the expandable surface element is that shape which provides the predetermined constant spacing between the inner spatial volume and the conformed surface of the resection cavity.” (Verhey Rep. at 9:22-24 (citing col. 5:47-61).) Examples of desired shapes described in the specification include a spherical balloon (FIG. 1) and a cylindrical balloon (FIG. 5), but the invention is not limited to any particular shape. (Col. 5:13-16.)

Q. “Predetermined Spacing” (Claims 3 & 25)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
No construction required or appropriate.	Indefinite because no information in patent re how to determine “predetermined spacing.” Also indefinite because spacing is between inner spatial volume and expandable surface element, i.e., deflated balloon or collapsed cage.

Cytec addresses the construction of this term in connection with its construction of the phrase “a predetermined spacing is provided between said inner spatial volume and the expandable surface element” below. Cytec believes that a separate construction of this term divorced from the context of the surrounding claim language is neither required nor appropriate.

R. “A Predetermined Spacing Is Provided Between Said Inner Spatial Volume And The Expandable Surface Element”/ “A Predetermined Spacing Between Said Inner Spatial Volume And The Expandable Surface Element” (Claims 3 & 25)

Cytec's Proposed Construction	Xoft's Proposed Construction
The distance between the inner spatial volume and the expandable surface element is determined in advance.	A predetermined spacing between inner spatial volume and deflated balloon or collapsed cage is indefinite.

Cytec believes that no construction of this term is required or appropriate and that the term is definite. The term has its ordinary and customary meaning and is understood by one of ordinary skill in the art without reference to intrinsic or extrinsic evidence, and there is no evidence of any intent by the inventors to impart a novel or special meaning to the term.

Contrary to Xoft's assertion, the term is not indefinite and has an ordinary and customary meaning to one skilled in the art. Dr. Verhey readily understood the term to mean that the spacing between the inner and outer volumes can be set to a predetermined value by modifying the level of inflation or expansion of one or both volumes. Although Xoft incorrectly suggests that the patent must describe that amount of spacing, a patent does not need to describe what one skilled in the art already knows and can practice. *See S3 Inc. v. nVidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001). One skilled in the art knows how to determine an appropriate “predetermined spacing.”

Moreover, to the extent Xoft contends that there can be no spacing between the inner volume and a deflated balloon or collapsed cage, that argument also fails. Such an argument is premised on the erroneous proposal that “expandable surface” be limited to a deflated or collapsed surface. Because that construction is inconsistent with the patent and must be rejected for the reasons set forth above (*see supra* at II.F), Xoft's indefiniteness argument must also fail.

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S. “Intraoperatively” (Claims 19 & 34)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
Intraoperatively Alternatively: during the surgical operation to remove proliferative tissue	After surgical removal of tumor but prior to closing the surgical site.

The parties appear to agree for the most part as to the meaning of “intraoperatively,” and Cytec could agree to Xoft’s proposed construction if only the construction does not include “closing the surgical site,” which is superfluous. “Intraoperatively” simply means during the surgical operation to remove the proliferative tissue. Whether the site is subsequently closed (*e.g.*, with sutures) is irrelevant.

T. “Solid Radiation Source” (Claim 16)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
A radiation source that has a fixed shape and volume, and is not deformable.	Solid radionuclide

Xoft again improperly attempts to limit a radiation source to a radionuclide. There are other sources of radiation besides radionuclides, and there is no basis in the intrinsic evidence for limiting the plain meaning of “radiation source” to a radionuclide. Moreover, Xoft neglects to define “solid,” which refers to the fact that the radiation source that has a fixed shape and volume and is not deformable. (*See* AHC at 1295 (“of definite shape and volume; not liquid or gaseous”); Verhey Rep. at 11:8-9.)

U. “The Prescribed Absorbed Dose Is Delivered To The Target Tissue In Substantially Three Dimensions” (Claim 18)

Cytec’s Proposed Construction	Xoft’s Proposed Construction
The prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose.	Prescribed absorbed dose is indefinite and substantially three dimensional is indefinite.

Contrary to Xoft's assertion, there is nothing indefinite about this limitation because one of ordinary skill in the art would understand what a prescribed absorbed dose is and how that dose can be delivered substantially in three dimensions. Dr. Verhey explains that this limitation relates to the fact that, once the outer chamber is expanded, the tissue in contact with the chamber conforms to the shape of the chamber, thereby assuring that all points within the tissue that are at a fixed distance from the wall of the surgical cavity will receive the identical dose. (Verhey Rep. at 11:12-15.) In this manner, the prescribed dose is delivered to the target tissue at the depth of interest substantially in all three dimensions, as opposed to being delivered in only two dimensions (to all points on a plane) or one dimension (to all points along a line). The limitation is clear, not indefinite, and should be given its ordinary meaning.

CONCLUSION

For the reasons stated above, this Court should adopt Cytac's proposed constructions of the disputed terms of the '813 and '204 patents, and reject Xoft's proposed constructions and indefiniteness arguments.

Respectfully submitted,

DATED: November 9, 2006

HOWREY LLP

By: /s/ Henry C. Su
Henry C. Su

Attorneys for Defendants CYTYC CORPORATION and
CYTYC SURGICAL PRODUCTS II, INC.

CERTIFICATE OF SERVICE

As required by Civil Local Rule 5-6(a)(2), the undersigned hereby certifies that on November 9, 2006, a true and correct copy of:

**DEFENDANT AND COUNTERCLAIMANT CYTYC CORPORATION'S
OPENING CLAIM CONSTRUCTION BRIEF (PAT. L.R. 4-5(a))**

was served on the following counsel of record for Xoft, Inc. electronically through this Court's Electronic Case Filing System, in accordance with Civil Local Rule 5-5(b):

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EXHIBIT F

E-FILED on 4/27/07

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

XOFT, INC.,

Plaintiff,

v.

CYTYC CORPORATION; and PROXIMA
THERAPEUTICS, INC.,

Defendants.

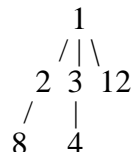
No. C-05-05312 RMW

CLAIM CONSTRUCTION ORDER

[Re Docket Nos. 48, 50, 53]

Xoft, Inc. sued Cytec Corporation and one of its subsidiaries, Cytec Surgical Products II, Inc., (collectively "Cytec") for a declaratory judgment of non-infringement and invalidity of U.S. Patent Nos. 5,913,813 and 6,413,204. Cytec responded by filing counterclaims for infringement of the same patents and currently asserts that Xoft infringes six claims of the '813 patent¹ and twenty

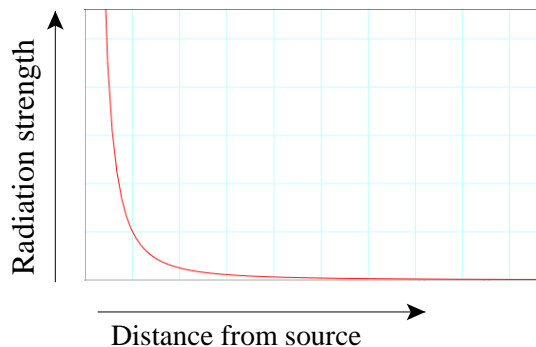
¹ Cytec asserts claims 1, 2, 3, 4, 8, and 12. Claim 1 is an apparatus claim and the only independent claim of the '813 patent. Claims 2, 3, and 12 depend directly from claim 1. Claim 4 depends from claim 3, and claim 8 depends from claim 2. The following is a graphic representation of the relationship of the asserted claims:



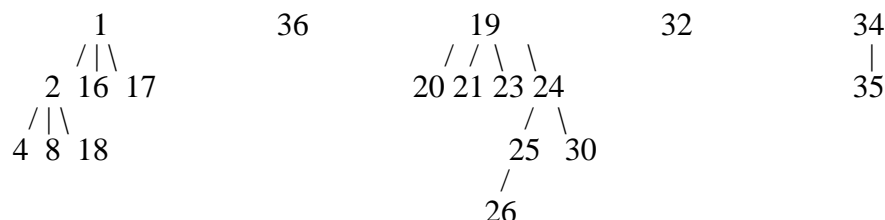
claims of the '204 patent². The application for the '204 patent was filed as a continuation-in-part of the '813 patent; the former purports to incorporate by reference the latter. '204 patent, col. 1, ll. 10-11. The parties seek construction of eight terms or phrases from the '813 patent and twenty-one terms or phrases from the '204 patent.

I. BACKGROUND

The patents-in-suit are directed to methods and apparatus for treatment of proliferative tissue diseases. The prior art discloses that a radiation source can be implanted at a tumor site to irradiate any remaining diseased tissue; this process is known as interstitial brachytherapy. The parties agree that for the purposes of this suit, the strength of radiation may be assumed to decrease with the square of the distance from the radiation source. The graph of the equation $y = I / x^2$ thus can be used as an approximation of the relationship between the radiation strength and distance. The graph, shown below, illustrates that the radiation strength close to the radiation source is disproportionately higher than that at a relatively small distance away from the radiation source.

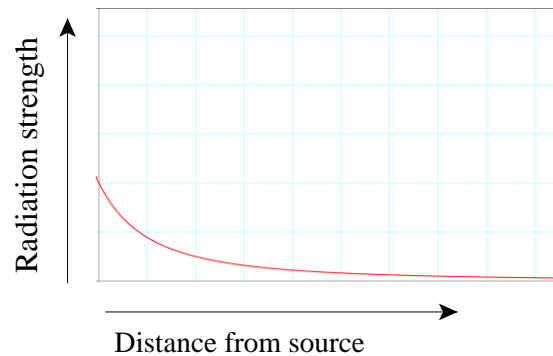


² Cytoc asserts claims 1, 2, 3, 4, 8, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 30, 32, 34, 35, and 36 of the '204 patent. Claims 1 and 36 are the only independent apparatus claims. From claim 1 depend claims 2, 16, and 17. From claim 2 depend claims 4, 8, and 18. Claims 19, 32, and 34 are independent method claims. Claims 20, 21, 23, and 24 all depend from claim 19. Claim 25 depends from claim 24, and claim 26 depends from claim 25. Claim 30 also depends from claim 24. Claim 35 depends from claim 34. The following is a graphic representation of the relationship of the asserted claims:



This shows one of the problems encountered in radiation therapy, namely, that tissue close to the radiation source may get more radiation than a physician would prefer. When using interstitial therapy, a physician may wish to give all tissue within a certain distance—say, for example, 3 centimeters—from the tumor site a certain dose of radiation. However, tissue closer to the tumor site—say, 1 centimeter—will receive a much higher dose of radiation because of the inverse-square relationship. This means that healthy tissue near the tumor site may be killed by the radiation, which is an undesirable result.

Following the teachings of the patents-in-suit, the very high levels of radiation near the source can be avoided by simple mechanical means. Surrounding the radiation source on all sides with empty space (or some material other than living tissue) prevents the highest levels of radiation from affecting living tissue, giving the tissue a radiation dose profile that looks something like this:



II. ANALYSIS

A. Terms of the '813 patent

"Inner spatial volume"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
A region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device

The summary of the invention provides that

it is possible to deliver a desired radiation dose at a predetermined radial distance from a source of radioactivity by providing a first spacial³ volume at the distal end of a catheter and a second spatial volume defined by a surrounding of the first spatial

³ Presumably all occurrences of "spacial" in the '813 patent should be read as "spatial."

volume by a polymeric film wall where the distance from the spatial volume⁴ and the wall is maintained substantially constant over their entire surfaces. One of the inner and outer volumes is filled with either a fluid or a solid containing a radionuclide(s) while the other of the two volumes is made to contain either a low radiation absorbing material, e.g., air or even a more absorptive material, such as an x-ray contrast fluid. Where the radioactive material comprises the core, the surrounding radiation absorbing material serves to control the radial profile of the radioactive emissions from the particular one of the inner and outer volumes containing the radionuclide(s) so as to provide a more radially uniform radiation dosage in a predetermined volume surrounding the outer chamber. Where the core contains the absorbent material, the radial depth of penetration of the radiation can be tailored by controlling the core size.

'813 patent, col. 1, l. 50-col. 2, l. 3. The first two claims of the '813 patent read:

1. Apparatus for delivering radioactive emissions to a body location with a uniform radiation profile, comprising:

- (a) a catheter body member having a proximal end and distal end;
- (b) an inner spatial volume disposed proximate the distal end of the catheter body member;
- (c) an outer, closed, inflatable, chamber defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall;
- (d) a material containing a radionuclide(s) disposed in one of the inner spatial volume and outer chamber; and
- (e) means disposed in the other of the inner spatial volume and outer chamber for rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber containing the radionuclides.

2. The apparatus as in claim 1 wherein said inner spatial volume is an inner closed, chamber defined by a further radiation transparent wall.

'813 patent, col. 4, ll. 32-54. Since all claims of this patent other than claim 1 depend from claim 1, construction of "inner spatial volume" is critical.

In most embodiments of the invention disclosed in the patent specification, the inner spatial volume is a region of space surrounded by an outer spatial volume that is defined by a closed inflatable chamber. *See* '813 patent, col. 2, ll. 44-63; col. 3, ll. 9-16, 42-48; col. 4, ll. 16-20; figs. 1,

⁴ Presumably this "spatial volume" should be taken to be the first spatial volume, which would mean that the polymeric film wall forms the outer boundary of the second spatial volume and that the second spatial volume is of a uniform thickness on all sides of the first spatial volume. Such a reading would comport with claim 1(c).

3-5. However, the patentee drafted the claims in such a way as to make clear that the inner spatial volume was not necessarily so limited:

Those skilled in the art will appreciate that instead of having the inner spatial volume **30** defined by a generally spherical polymeric film wall as at **32**, the catheter body member **12** may have a solid spherical radiation emitting material in which event that solid sphere would be surrounded with the outer spherical wall **36** with the spatial volume therebetween occupied by a radioactive ray absorbent material, such as air, water or a contrast material.

'813 patent, col. 2, ll. 55-63.

Although somewhat awkwardly worded, the language of the patent allows for the inner volume to be defined by something other than a region enclosed by a polymeric wall. As Cytyc points out, Xofter's construction conflates the boundary of the volume with the volume itself. Cytyc's proposed construction, however, is a paraphrasing of the language of claim 1 that only clarifies a little the language of the patent. Furthermore, Cytyc's proposed construction would exclude an inner volume defined by a solid sphere, and thus cannot be correct.

Xofter objects that an abstract concept like a region of space cannot be part of an apparatus. Xofter is correct. However, the language of the patent does not imply that the inner volume is ever defined by something other than a physical object. In all embodiments of the invention disclosed in the '813 patent, the boundary of the inner volume is either a polymeric film wall or the edge of a solid sphere. Furthermore, it would seem difficult to fill one volume with radioactive liquid and the other with another fluid if the two volumes were not separated by some structure (which would necessarily be the outer boundary of the inner spatial volume.) See '813 patent, col. 1, ll. 57-62. The patent is even entitled "Double-Wall Balloon Catheter for Treatment of Proliferative Tissue." Xofter's expert, Dr. Lovoi, acknowledged that an "inner spatial volume" is a volume that is inside another volume. Lovoi Dep. at 101:25-102:7. The court defines "inner spatial volume" as "a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the edge of a solid radionuclide sphere."

<i>Claim Language</i>	<i>Court's Construction</i>
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere

"Outer, closed, inflatable chamber"

<i>Cytec's proposed construction</i> (no construction required)	<i>Xoft's proposed construction</i> Inflatable balloon, i.e., deflated balloon
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Part (c) of claim 1 explains that the "outer, closed, inflatable chamber" is "defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall." '813 patent, col. 4, ll. 40-45. The preferred embodiment recites a similar structure: "Surrounding the spatial volume **30** is an outer chamber **34** defined by an outer polymeric film wall **36** that is appropriately spaced from the wall **32** of the inner chamber **30** when the two chambers are inflated or otherwise filled and supported." '813 patent, col. 2, ll. 37-41. There is no support in the patent for Xoft's argument that "outer, closed, inflatable chamber" should be limited to only a balloon in a deflated state. The court will therefore adopt Cytec's proposal and not otherwise define this term.

<i>Claim Language</i>	<i>Court's Construction</i>
"outer, closed, inflatable chamber"	outer, closed, inflatable chamber

"Predetermined constant spacing"

<i>Cytec's proposed construction</i> (no construction required)	<i>Xoft's proposed construction</i> (indefinite)
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"Predetermined constant spacing between said inner spatial volume and radiation transparent wall"

<i>Cytec's proposed construction</i> The spacing between the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, can be made constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical	<i>Xoft's proposed construction</i> (indefinite)
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Xoft argues that the '813 patent is indefinite because it does not disclose how one "predetermines" the amount of spacing. Xoft points out that the spacing between the edges of the inner and outer volumes may change as parts of the apparatus are inflated or deflated, so the spacing is not constant. Cytec's expert explained that "predetermined constant spacing" means that "the

spacing between the inner spatial volume and the wall of the outer inflatable chamber can be made constant in all directions if the outer chamber is spherical, or constant along a radial direction if non-spherical, whenever the outer chamber is inflated." Su Decl. (dkt. # 49), Ex. D (Verhey Decl.) at 7 (citations omitted). Cytyc also argues that "[o]ne skilled in the art knows how to determine an appropriate 'predetermined constant spacing' and Xoft provides no evidence, testimony, or case law to the contrary. Xoft cannot possibly show that the term is indefinite by clear and convincing evidence." Reply Br. (dkt. # 53) at 15.

Because 35 U.S.C. § 282 gives a patent "a statutory presumption of validity," a challenger bears the burden of proving "by clear and convincing evidence" that a patent is invalid. *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1336-37 (Fed. Cir. 2006). "[P]atent documents need not include subject matter that is known in the field of the invention." *S3 Inc. v. NVIDIA Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001). From the testimony of Dr. Verhey, it appears that one skilled in the art would know how to "predetermine" the amount of spacing.⁵ See Tr. at 56-61, 85-89. Xoft offered no evidence suggesting otherwise. As the burden of proof is Xoft's, its indefiniteness argument necessarily fails given the absence of supporting evidence. The court will therefore adopt Cytyc's proposed construction of "predetermined constant spacing between said inner spatial volume and radiation transparent wall" modified only to make the definition easier to understand. A separate construction for "predetermined constant spacing" is not necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"predetermined constant spacing"	(no construction necessary)
"predetermined constant spacing between said inner spatial volume and radiation transparent wall"	spacing predetermined by one skilled in the art between the wall or edge of the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, which is constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical

⁵ Xoft argues that the size of the cavity determines the size of the apparatus when fully inflated, but this alone does not determine the spacing between the inner spatial volume and the wall of the outer chamber.

"Rendering uniform"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	Making the same, i.e., causing to have the same value or characteristic at all points.

"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
Function: Modifying the ratio of the absorbed dose at a depth of interest in the target tissue to the absorbed dose at the surface of the tissue. Structure: A radiation absorbing or attenuating material, <i>e.g.</i> , air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate.	Function: Making the dose along a radius extending from the radionuclide outwardly from the outer chamber wall the same at every point on the radius. Structure: No such means disclosed in '813 patent, means for making more uniform disclosed as substance within outer chamber.

Xoft's argument is that "uniform" must be taken literally, and the apparatus must produce radiation that does not decrease in strength with increasing distance from the source.⁶ The parties do not dispute that Xoft's construction would require a physical impossibility; the strength of radiation necessarily decreases with distance from its source. Xoft, however, seeks to interpret "uniform" in a vacuum. The meaning of a particular word in a claim must be interpreted in light of the rest of the patent. *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1303 (Fed. Cir. 1997).

While the patent could have been drafted with more clarity, it is readily apparent that the patentee did not contemplate absolute uniformity. Figure 4 of the patent (reproduced below) is a comparison between the distance versus radiation dose plots of two scenarios. Line **40** shows the radiation dose that would result if chamber **36** were filled with a radioactive fluid. '813 patent, col. 3, ll. 20-24. Line **42** shows the radiation dose that would result if, following the teachings of the patent, the same radioactive fluid were contained only in chamber **32**. '813 patent, col. 3, ll. 24-28. As explained in the patent, "Comparing the plots **40** and **42**, by providing the concentric arrangement depicted, the absorbed dose profile in the space between the 2 cm site and the wall of the outer balloon is maintained much more uniform, thus preventing over-treatment of body tissue at

⁶ Xoft also stated that it would "submit a Motion for Summary Judgment on this issue prior to the conduct of the *Markman* hearing," Responsive Br. (dkt. # 50) at 14, but did not do so.

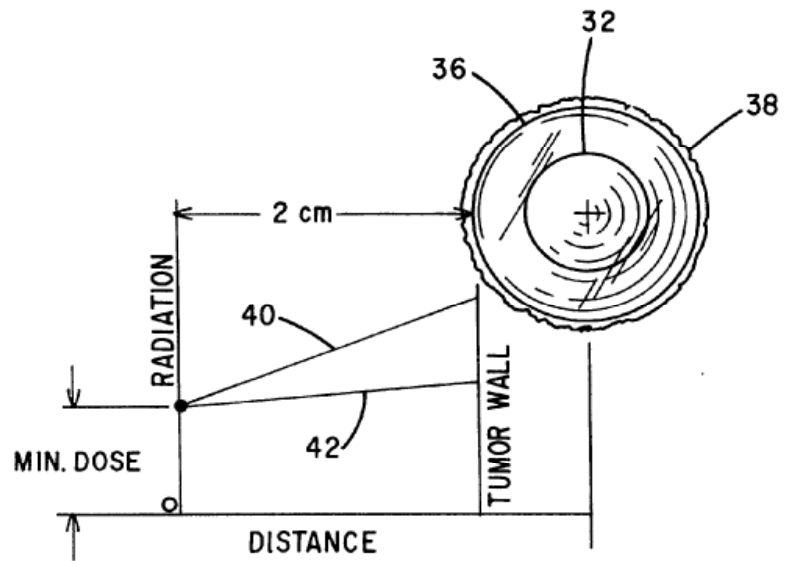
or close to the outer wall **36** of the instrument." '813 patent, col. 3, ll. 28-33.

The patentee obviously did not expect absolute uniformity of radiation dosing. To interpret "uniform" in the manner urged by Xoft would go against the clear intent of the patentee. In *Bausch & Lomb, Inc. v. Barnes-*

Hind/Hydrocurve, Inc., 796 F.2d

443 (Fed. Cir. 1986), the defendant made a similar argument regarding the patentee's use of the term "smooth" with respect to the edges of contact lenses. The Federal Circuit looked to the intrinsic evidence and found that "smooth" did not mean absolutely ridge free but rather that it meant "smooth enough to serve the inventor's purposes, *i.e.*, not to inflame or irritate the eyelid of the wearer or be perceived by him at all when in place." *Id.* at 450. In this case, the inventor's purpose was to deliver radiation more uniformly than had previously been done, "thus preventing over-treatment of body tissue at or close to the outer wall . . . of the instrument." '813 patent, col. 3, ll. 28-32. The court will therefore define "rendering uniform" to mean to make the absorbed dose of radiation more uniform in order to prevent over-treatment of body tissue at or close to the outer wall of the instrument.

Since limitation language "means . . . for rendering uniform the radial absorbed dose profile of the emissions" is in means-plus-function format, the function must be construed and the corresponding structure or its equivalent identified in the specification. *BBA Nonwovens Simpsonville, Inc. v. Superior Nonwovens, L.C.C.*, 303 F.3d 1332, 1343 (Fed. Cir. 2002). As discussed, Xoft's definition of the function requires absolute uniformity which is not possible and which is not what the patent requires or the inventor intended. Cytyc's proposed definition construes the function as "modifying the ratio of the absorbed dose at a depth of interest in the target tissue to



the absorbed dose at the surface tissue." Although this appears to be a function of the invention, Cytec's definition is too broad because it encompasses absorbed doses at the surface tissue that are not substantially uniform to absorbed doses at the target tissue. In other words, Cytec's definition would not only encompass the radiation dose profile of line 42 above, but would also encompass the radiation dose profile of line 40. Furthermore, all radiation dose profiles between line 40 and line 42 that result in over-treatment of the surface tissue would also be included under Cytec's definition. A more accurate construction of the function would require the absorbed dose at the target tissue and the absorbed dose at the surface tissue to be more uniform to prevent over-treatment of the surface tissue. Thus, the court defines the function of the "means . . . for rendering uniform the radial absorbed dose profile of the emissions" as making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument.

Cytec also identifies a radiation-absorbing or -attenuating material as the corresponding structure. At the claim construction hearing, Xoft argued that the uniformity of the radiation dose curve is solely affected by distance from the radiation source; the parties agree that this is true. *See* Tr. at 60-61. Although the composition of the material is not critical to the function, the radiation-absorbing or -attenuating material provides the distance necessary for achieving the uniformity in radiation dose curve. Thus, the court construes the language consistently with Cytec's position.

<i>Claim Language</i>	<i>Court's Construction</i>
"rendering uniform"	to make the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument
"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"	<p>Function: Making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument.</p> <p>Structure: A radiation absorbing or attenuating material, <i>e.g.</i>, air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate or their equivalents.</p>

"The radioactive material"

<i>Cytoc's proposed construction</i>	<i>Xoft's proposed construction</i>
The material of claim 1 containing a radionuclide.	(indefinite)

Claim 8 of the patent covers "[t]he apparatus as in claim 2 wherein the inner chamber contains the radioactive material." Claim 2 depends from claim 1. The parties dispute whether "a material containing a radionuclide(s)" suffices as an antecedent basis for "the radioactive material." It is readily apparent that the "radioactive material" in claim 8 refers back to "a material containing a radionuclide" described in claim 1, since "radionuclide" is the only radioactive material mentioned in claim 1. Anyone skilled in the art would so conclude. Xoft's contention that the term "radioactive material" is indefinite because it contains no antecedent basis is without merit. Xoft offers no authority suggesting that the antecedent basis of a term used in a dependent claim must be stated in identical words.⁷ The court, therefore construes "the radioactive material" in claim 8 to be the "radionuclide(s)" referred to in claim 1.

<i>Claim Language</i>	<i>Court's Construction</i>
"The radioactive material"	The material of claim 1 containing a radionuclide.

"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"

<i>Cytoc's proposed construction</i>	<i>Xoft's proposed construction</i>
A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired dose profile that is the sum of the radiation profiles of the plurality of particles.	Static array of solid radioactive particles each placed in a single location and mounted on distal ends of separate wires. Desired composite radiation profile" is indefinite.

Claim 12 of the patent is directed to "[t]he apparatus as in claim 1 wherein the material containing a radionuclide comprises a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile." Xoft argues claim 12 is indefinite on two grounds: first, that "desired composite radiation profile" is not

⁷ At the *Markman* hearing, Xoft stated that it would provide a citation to such supporting authority. Tr. at 64. Xoft, however, has not done so.

defined, and second, that "inner spatial volume" is indefinite because no physical structure bounds it. The court rejects Xoft's second argument for the reasons given when construing "inner spatial volume" above. The court rejects Xoft's first argument because it presents no evidence that one skilled in the art would not understand "desired composite radiation profile."⁸ Cytac's proposed construction does not clarify the meaning of claim 12. However, since the language is understandable as is, no construction of "a plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile" is necessary or appropriate.

<i>Claim Language</i>	<i>Court's Construction</i>
"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"	(no construction needed)

B. Terms of the '204 patent

Claim 1 of the '204 patent is similar to claim 1 of the '813 patent. Claim 1 of the '204 patent describes:

An interstitial brachytherapy apparatus for delivering radioactive emissions to an internal body location comprising:

- (a) a catheter body member having a proximal end and distal end;
- (b) an inner spatial volume disposed proximate to the distal end of the catheter body member;
- (c) an outer spatial volume defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume; and
- (d) a radiation source disposed in the inner spatial volume and generating a three-dimensional isodose profile that is substantially similar in shape to the expandable surface element.

⁸ It would seem that for one skilled in the art, it would be a relatively simple matter to add up the individual radiation profiles of individual particles. *See* Tr. at 75-76.

"Interstitial"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	Site in natural or surgically created cavity in body.

"Brachytherapy"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
Radiation therapy delivered by a spatially confined radiation source at or near the site of the diseased tissue.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor or other proliferative tissue disease site.

"Interstitial brachytherapy"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
Brachytherapy applied directly to the interspaces of a body tissue, where the interspaces are not naturally occurring.	Radiation therapy delivered by a spatially confined radionuclide at or near a tumor site in a natural or surgically created cavity in a body.

Cytec argues that "interstitial" and "brachytherapy" should be constructed together; Xoft seeks a separate construction for each word. Cytec also complains that Xoft seeks to limit "brachytherapy" to radionuclides, arguing that the definition should encompass any radiation source. However, the patent provides a clear definition of "brachytherapy": "The term 'brachytherapy,' as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." '204 patent, col. 1, ll. 30-33. Here, the patentee clearly acted as his own lexicographer, and Cytec's arguments for a broader definition do not acknowledge this clear definition. The court construes "brachytherapy" to mean "radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site."⁹

Xoft argues that "interstitial" means any body cavity, while Cytec argues that "interstitial" should be limited to only non-naturally-occurring cavities. As Xoft points out, one medical dictionary defines "interstitial" as "1. Placed or lying between. 2. Pert. to

⁹ This definition does not resolve the parties' dispute over whether "radioactive material" should be read to encompass only "radionuclides" (as Xoft wishes) or any "radiation source" (as Cytec urges). As the parties have separately sought construction of "radioactive material," the court will address construction of that phrase below.

1 interstices or spaces within an organ or tissue." TABER'S CYCLOPEDIA MEDICAL
2 DICTIONARY, 1007 (Clayton M. Thomas, ed., 17th ed. 1993). Although not cited by the
3 parties, a British oncology text indicates that "interstitial" has a particular meaning in the
4 field of the invention:

5 Two main techniques are used for the delivery of radiation which is given
6 either as an external beam or as short range radiation from an implanted radioactive
7 source. External beam radiation usually involves megavoltage produced by linear
8 accelerator as photons or electrons or from cobalt sources in the form of relative low
9 energy X-rays or gamma rays. The latter are often used to treat relatively superficial
10 lesions such as basal cell carcinoma or recurrences within the skin. High energy
11 radiation can be used to treat deeply located lesions such as prostatic carcinomas
12 without delivering an excessive dose to adjacent normal tissue. . . .

13 Interstitial implant irradiation gives a high local dose to the tumour and
14 usually employs sources such as radium, iridium, or caesium used in the form of
15 needles or wires implanted in the tumour. This technique is widely used in the
16 treatment of head and neck cancers to deliver a high tumour dose without irradiation
17 to sensitive organs such as the lens of the eye or the spinal cord.

18 I.S. Fentiman, *The local Treatment of Cancer*, INTRODUCTION TO THE CELLULAR & MOLECULAR
19 BIOLOGY OF CANCER, 434, 446 (L.M. Franks & N.M. Teich, eds., 2d ed. 1991).

20 However, Cytac points out that regardless of any generally-accepted meaning of "interstitial"
21 in the field of the invention, the patentee limited "interstitial" during prosecution to refer to only
22 surgically-created cavities (and similarly defined "intercavitary" to refer to natural body cavities):

23 Turning to the cited prior art, the Ishiwara device comprises a
24 thermotherapeutic apparatus having a catheter body member, an inner lumen
25 surrounded by an outer lumen, and a radiation source contained within the inner
26 lumen. . . . Ishiwara's apparatus is inserted into a body cavity. Hence, the apparatus
27 does not provide *interstitial* radiation treatment, as Applicant's invention requires, but
28 rather intercavitary radiation treatment.

Su Decl. (dkt. # 49), Ex. C (Amendment & Resp.) at 11 (citations omitted). This is consistent with
the background section of the patent, which mentions surgical cavities several times but not natural
ones. '204 patent, col. 1, ll. 19, 23, 25, 63, col. 2, l. 1. Also, although the summary section does not
specify what type of cavities the apparatus claims are directed to, the summary makes clear that the
method claims are directed to a method that "includes surgically creating access to the proliferating
tissue within a patient and surgically resecting at least a portion of the proliferating tissue to create a
resection cavity within body tissue." *Id.*, col. 3, ll. 3-6.

The parties did not brief the issue of how much weight the court should afford the prosecution history in this instance.¹⁰ The Federal Circuit has instructed that "[a]lthough prosecution history can be a useful tool for interpreting claim terms, it cannot be used to limit the scope of a claim unless the applicant took a position before the PTO that would lead a competitor to believe that the applicant had disavowed coverage of the relevant subject matter." *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002). Here, the patentee clearly disavowed coverage of intercavitary radiation treatment when arguing to the PTO. Given the

¹⁰ In its recent *en banc* explanation of the evidence to be used in construing claims, the Federal Circuit devoted a paragraph to prosecution history:

In addition to consulting the specification, we have held that a court "should also consider the patent's prosecution history, if it is in evidence." *Markman*, 52 F.3d at 980; *see also Graham v. John Deere Co.*, 383 U.S. 1, 33, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966) ("[A]n invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office."). The prosecution history, which we have designated as part of the "intrinsic evidence," consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent. *Autogiro*, 384 F.2d at 399. Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent. *See Lemelson v. Gen. Mills, Inc.*, 968 F.2d 1202, 1206 (Fed. Cir. 1992). Furthermore, like the specification, the prosecution history was created by the patentee in attempting to explain and obtain the patent. Yet because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes. *See Inverness Med. Switz. GmbH v. Warner Lambert Co.*, 309 F.3d 1373, 1380-82 (Fed. Cir. 2002) (the ambiguity of the prosecution history made it less relevant to claim construction); *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1580 (Fed. Cir. 1996) (the ambiguity of the prosecution history made it "unhelpful as an interpretive resource" for claim construction). Nonetheless, the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be. *Vitronics*, 90 F.3d at 1582-83; *see also Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) ("The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution.'"), quoting *ZMI Corp. v. Cardiac Resuscitator Corp.*, 844 F.2d 1576, 1580 (Fed. Cir. 1988); *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995).

Phillips v. AWH Corp., 415 F.3d 1303, 1317 (Fed. Cir. 2005) (*en banc*).

intrinsic evidence is of primary importance¹¹ and all supports Cytyc's position, the court construes "interstitial" to mean "involving a surgically-created cavity in a body."

In light of the constructions of "interstitial" and "brachytherapy" above, no further construction of "interstitial brachytherapy" is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"interstitial"	involving a surgically-created cavity in a body
"brachytherapy"	radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site
"interstitial brachytherapy"	(no construction necessary)

"Inner spatial volume"

<i>Cytyc's proposed construction</i>	<i>Xoft's proposed construction</i>
A region of space surrounded by an outer spatial volume that is defined by an expandable surface element	Inner balloon in two-balloon device or spherical solid radionuclide in one-balloon device.

The phrase "inner spatial volume" appears in both patents-in-suit. The parties' arguments regarding the meaning of "inner spatial volume" are similar for each patent. The relevant portions of the specification are the same, and, additionally, the '204 patent purports to incorporate by reference the '813 patent. '204 patent, col. 1, ll. 10-11. The court will therefore construe "inner spatial volume" in the '204 patent in the same manner as for the '813 patent.

<i>Claim Language</i>	<i>Court's Construction</i>
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere.

¹¹ The extrinsic evidence that Cytyc used "intercavitary" in literature and advertising in a manner that encompasses the definitions of "interstitial" and "intercavitary" it advances now, *see* Tr. at 93, is of little weight in this situation. Similarly, evidence presented by Cytyc that Xoft represented to the FDA that the term "interstitial" "is a more appropriate word for a cavity that is surgically created as compared to a natural body cavity," (*see* Decl. of Henry Su Supp. Cytyc's Supplemental Claim Construction Br., Ex. A, is not entitled to significant weight although it does suggest that one skilled in the art construes the term as Cytyc proposes.

"Outer spatial volume"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required) or A region of space defined by an expandable surface element and surrounding an inner spatial volume.	Balloon or cage.

The phrase "outer spatial volume" in the '204 patent is analogous to the "outer, closed, inflatable chamber" of the '813 patent. The "outer spatial volume" is also explained in a similar manner; it is "defined by an expandable surface element disposed proximate to the distal end of the body member in a surrounding relation to the inner spatial volume." '204 patent, col. 8, ll. 22-25. Xoft again confuses the concepts of a volume with the boundary of a volume. Cytec's proposed construction is congruent with the language of claim 1 of the '204 patent, so the court will construe "outer spatial volume" as "a region of space defined by an expandable surface element and surrounding an inner spatial volume."

<i>Claim Language</i>	<i>Court's Construction</i>
"outer spatial volume"	a region of space defined by an expandable surface element and surrounding an inner spatial volume

"Expandable surface element"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required) or A device that can be expanded or inflated, such as an expandable cage or an inflatable balloon.	Deflated balloon or collapsed cage.

Xoft's basic argument is that "expandable surface element" must be a deflated structure because once something is fully inflated, it is no longer expandable. Xoft also points out that part (d) of claim 1 refers to the "isodose profile" being "substantially similar in shape to the expandable surface element" without specifying whether the expandable surface element is fully expanded. It is apparent that the patentee intended "expandable surface element" to refer to a structure whether it was fully inflated or not. Xoft's proposed construction would have this element wink out of

existence at full inflation, leaving the "outer spatial volume" unbounded and giving the "isodose profile" no shape. The court agrees with Cytac that no construction of the term is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"expandable surface element"	(no construction needed)

"Radiation source"

<i>Cytac's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	radionuclide

The patent provides a clear definition of "brachytherapy": "The term 'brachytherapy,' as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." All asserted independent claims of the '204 patent contain the phrase "interstitial brachytherapy," which the court has construed as "radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site." Cytac's argument that "radiation source" should not be constructed to exclude any radiation sources must be rejected; the claims clearly do not contemplate a radiation source other than "radioactive material."

There is still, however, the question of whether "radioactive material" means the same thing as Xoft's proposed construction of "radionuclide."¹² In describing the preferred embodiment, the patent says: "[t]he inner volume **30** is then filled with a material containing a predetermined radionuclide, for example, I-125, I-131, Yb-169 or other source of radiation, such as radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays." '204 patent, col. 4, ll. 9-13 (emphasis added). Since all the examples of sources of radiation given in the specification are radionuclides, the patentee appears to have intended to define "radioactive material" as "radionuclides." Cytac argued at the *Markman* hearing that "or other therapeutic rays" could refer to other sources such as x-rays. The words "or other therapeutic rays," however, clearly refers to types

¹² The parties have agreed that "radionuclide" means "an isotope that undergoes radioactive decay."

of radionuclides. Cytyc's construction would require the patentee to have inserted the word "or" before "gamma radiation," indicating the end of the list of types of radionuclides.¹³

Dictionary definitions are consistent with construing "radiation source" as a "radionuclide." One definition of "radioactive" is "[a] descriptive term for a material made up of atoms in which radioactivity occurs." AMERICAN HERITAGE NEW DICTIONARY OF CULTURAL LITERACY (3d ed. 2006). A medical dictionary provided by Xoft defines "radioactive" as "giving off radiation as the result of the disintegration of the nucleus of an atom." MOSBY'S MEDICAL, NURSING, AND ALLIED HEALTH DICTIONARY, 1326 (Kenneth N. Anderson *et al.* eds., 4th ed. 1994). Cytyc has not presented evidence that one skilled in this art would understand "radioactive material" any differently. The court agrees with Xoft—the term "radioactive" in the context of the '204 patent does not encompass such radiation sources as x-ray tubes, and "radiation source" therefore should be taken to mean "radionuclide."

<i>Claim Language</i>	<i>Court's Construction</i>
"radiation source"	radionuclide

"Minimum prescribed dose"

<i>Cytyc's proposed construction</i>	<i>Xoft's proposed construction</i>
Minimum prescribed dose received within a target tissue for delivering therapeutic effects.	Minimum dose needed to treat cancer cells.

The parties have requested construction of the phrase "minimum prescribed dose" and point out that the term appears in claims 2, 18, 24, 32, and 36 of the '204 patent. The parties do not argue that the term should be construed differently for different claims. However, claims 2, 24, 32, and 36 contain the phrase "minimum prescribed absorbed dose," and claim 18 contains the phrase "prescribed absorbed dose." These inconsistencies seem irrelevant, however, because the parties'

¹³ Cytyc also stated that this was an "Oxford comma" issue. Tr. at 137-38. However, in the sentence at issue, the Oxford comma is the one after "gamma radiation." Whether it is present does not alter the meaning of the sentence. Cytyc also argued that "we're in the land of eats, shoots and leaves." If Cytyc was referring to a book of such title, the court does not see how that would support Cytyc's argument; the theme of *Eats, Shoots & Leaves* is that punctuation should be used correctly. See Lynne Truss, *Eats, Shoots & Leaves: The Zero Tolerance Approach to Punctuation* (2004).

dispute is whether any such doses should be limited to treatment of cancer cells or allowed to cover any potential therapeutic effects. The court's construction of "brachytherapy" limits the claims to treatments "at or near a tumor or other proliferative tissue disease site." Xoft's proposed construction is too narrow, and Cytyc's is too broad. However, in light of the construction of "brachytherapy," no construction of "minimum prescribed dose" or similar phrases is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"minimum prescribed dose"	(no construction necessary)

"Delivering a prescribed absorbed dose"

<i>Cytyc's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	(indefinite)

Xoft argues that the patent does not reveal how one goes about prescribing a dose using the device, and that the phrase "delivering a prescribed absorbed dose" is therefore fatally indefinite. The '204 patent, however, describes a tool for treating proliferative tissue disease. A patent could adequately describe and claim a new apparatus or method for making the corrective curves in contact lenses, but a description of the particular curves a patient might require would not be necessary. If those skilled in the art would know how to use the disclosed invention, describing how to use it is unnecessary—the patentee merely needs to adequately describe the invention. Since Xoft bears the burden of proving that those skilled in the art would not know how to use the tool or method described in the patent and has presented no evidence on the subject, the court rejects Xoft's contention that the phrase is indefinite. No construction is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"delivering a prescribed absorbed dose"	(no construction necessary)

"The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"

<i>Cytyc's proposed construction</i>	<i>Xoft's proposed construction</i>
The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose for delivering	(indefinite)

"The inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
Configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose for delivering therapeutic effects to a target tissue.	(indefinite)

The phrases "the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose" and "configuring the inner and outer spatial volumes to provide a minimum prescribed absorbed dose" are not indefinite for essentially the same reasons given in the previous section. As Cytec again appears to be attempting to impermissibly broaden its claims to capture any therapeutic effect, despite the clear limitation provided by the patentee's definition of "brachytherapy," the court also cannot adopt Cytec's proposed construction. No construction of the disputed language is necessary in light of the court's construction of other terms in the patent.

<i>Claim Language</i>	<i>Court's Construction</i>
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)

"A minimum distance outward from the outer spatial volume expandable surface"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	(indefinite)

Claims 2, 24, 32, and 36 all include the phrase "the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface."¹⁴ Xoft asserts that "minimum distance" is indefinite in this context because the patent does not explain how the minimum distance is determined.

¹⁴ The court believes that one skilled in the art would understand that the patentee intended to define "target tissue" as the tissue "between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface." Taken literally, the patent explains the physical location where the act of defining "target tissue" takes place.

Here, "minimum" does not appear to add anything to the patent. The "target tissue" is the tissue outside of the outer chamber for a fixed distance in all directions, but this fixed distance or how one determines it are not explained. It seems that one skilled in the art would know how to determine the distance. *See* Tr. at 85-89. But the patent may as well read "a short distance outward" or "a determined distance outward" or merely "a distance outward."

Cytec claims that specification provides some guidance and that the minimum distance may in some instances be between half and one centimeter. The specification does state that

device A can readily be configured to provide a dose in a therapeutic range, say between 40 to 60 Gray, at a distance between 0.5 and 1.0 cm from the outer spatial volume for an outer spatial volume having a diameter of 4.0 cm and being in contact with the resection cavity wall.

'204 patent, col. 6, ll. 31-35. However, Cytec neglects to mention that "device A" is "an interstitial brachytherapy apparatus . . . such as those employed in U.S. Pat. No. 5,429,582, having a single spatial volume **50** filled with a radioactive material in solution." '204 patent, col. 6, ll. 3-7. In any case, this discussion does not use the phrases "target tissue" or "a minimum distance outward." Nevertheless, Xofter has presented no evidence that one skilled in the art would not understand the phrase "the target tissue being defined between the outer spatial volume expandable surface and a minimum distance outward from the outer spatial volume expandable surface." Xofter has not met its burden of proving by clear and convincing evidence that this language is indefinite, and the court finds that no construction is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"a minimum distance outward from the outer spatial volume expandable surface"	(no construction necessary)

"Controlled dose"

<i>Cytec's proposed construction</i>	<i>Xofter's proposed construction</i>
(no construction required)	(indefinite)

"To reduce or prevent necrosis in healthy tissue proximate to the expandable surface"

<i>Cytec's proposed construction</i>	<i>Xofter's proposed construction</i>
(no construction required)	(indefinite)

"Providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"

<i>Cytac's proposed construction</i>	<i>Xoft's proposed construction</i>
Controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface	(indefinite)

Xoft argues that the patent does not reveal how one goes about controlling a dose using the device and that "reducing necrosis" is a hopelessly vague concept, making the '204 patent indefinite. Xoft, however, has presented no evidence that one skilled in the art would not be able to understand the patent and has again failed to meet its burden of proof. The court will therefore adopt Cytac's construction proposals. "Providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue" means "controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface."

<i>Claim Language</i>	<i>Court's Construction</i>
"controlled dose"	(no separate construction necessary)
"to reduce or prevent necrosis in healthy tissue proximate to the expandable surface"	(no separate construction necessary)
"providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"	controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface

"Adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	(indefinite)

Xoft's contention that this phrase is indefinite springs from its argument that "expandable surface element" means "deflated balloon or cage." As the court has rejected Xoft's interpretation of "expandable surface element," no construction of "adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue" is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"	(no construction necessary)

"Desired shape of the expandable surface element"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	(indefinite)

Xoft has again presented no evidence to back up an argument that the phrase is indefinite and therefore again fails to carry its burden of proof. No construction of "desired shape of the expandable surface element" is necessary.

<i>Claim Language</i>	<i>Court's Construction</i>
"desired shape of the expandable surface element"	(no construction necessary)

"Predetermined spacing"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required)	(indefinite)

"A predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "A predetermined spacing between said inner spatial volume and the expandable surface element"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
The distance between the inner spatial volume and the expandable surface element is determined in advance	(indefinite)

Xoft's contention that these phrases are indefinite is based on its argument that "expandable surface element" means "deflated balloon or cage," and Xoft has again presented no evidence to back up arguments that the phrases are indefinite. No construction of "predetermined spacing" is necessary. The court will adopt Cytyc's proposals and define both of the long phrases ("a predetermined spacing is provided between said inner spatial volume and the expandable surface element" and "a predetermined spacing between said inner spatial volume and the expandable surface element") as "the distance between the inner spatial volume and the expandable surface element is determined in advance."

<i>Claim Language</i>	<i>Court's Construction</i>
"predetermined spacing"	(no construction necessary)
"a predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "a predetermined spacing between said inner spatial volume and the expandable surface element"	the distance between the inner spatial volume and the expandable surface element is determined in advance

"Intraoperatively"

<i>Cytyc's proposed construction</i>	<i>Xoft's proposed construction</i>
(no construction required) or During the surgical operation to remove proliferative tissue.	After surgical removal of tumor but prior to closing the surgical site

At the claim construction hearing, the parties appeared to agree on the definition of "interoperatively." *See* Tr. at 140. The previous apparent disagreement revolved around whether the surgical site could be closed before insertion of the catheter apparatus. The court understands that the parties agree that the catheter must be inserted before the surgical site is closed. The '204 patent at column 7, lines 55-64, specifically refers to the catheter being inserted "[f]ollowing tumor resection, but prior to closing the surgical site."

<i>Claim Language</i>	<i>Court's Construction</i>
"intraoperatively"	following tumor resection, but prior to closing the surgical site

"Solid radiation source"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
A radiation source that has a fixed shape and volume, and is not deformable	Solid radionuclide

The parties' primary dispute here is whether "radiation source" encompasses more than radionuclides, which the court addressed above to limit "radiation source" to radionuclides. Cytec presents a dictionary definition of "solid," namely, "of definite shape and volume; not liquid or gaseous," from the AMERICAN HERITAGE COLLEGE DICTIONARY, 1295 (3d ed. 1997). The court will therefore define "solid radiation source" as "a radionuclide of definite shape and volume; not liquid or gaseous."

<i>Claim Language</i>	<i>Court's Construction</i>
"solid radiation source"	a radionuclide of definite shape and volume; not liquid or gaseous

"The prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"

<i>Cytec's proposed construction</i>	<i>Xoft's proposed construction</i>
The prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose.	(indefinite)

Xoft contends that "prescribed absorbed dose" and "in substantially three dimensions" render "the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions" fatally indefinite. The court has already rejected Xoft's argument regarding "prescribed absorbed dose."

Xoft points to Cytec's expert's testimony that "there's no such thing as substantially three dimensions" because something is either three dimensional or not. Mulville Decl. (dkt. # 51), Ex. L (Verhey Decl.) at 153. Cytec points to Xoft's expert's testimony that he could envision a brachytherapy apparatus that delivered 99 percent of its radiation in a plane; Cytec claims such a flat radiation field would not be in substantially three dimensions. Though a closer question than some of Xoft's other indefiniteness contentions, the court nonetheless finds that Xoft has not shown by clear and convincing evidence that one skilled in the art would not understand "in substantially three

dimensions" in the manner put forth by Cytyc. The court therefore adopts Cytyc's proposed construction for "the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions," namely, "the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose."

<i>Claim Language</i>	<i>Court's Construction</i>
"the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"	the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose

III. ORDER

1. For the reasons given above, the court adopts the following claim construction as detailed in this order.

Term or phrase	Court's construction
"inner spatial volume"	a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide sphere.
"outer, closed, inflatable chamber"	outer, closed, inflatable chamber
"predetermined constant spacing"	(no construction necessary)
"predetermined constant spacing between said inner spatial volume and radiation transparent wall"	spacing predetermined by one skilled in the art between the wall or edge of the inner spatial volume and the radiation transparent wall of the outer, closed, inflatable chamber, when inflated, which is constant in all directions if the outer chamber is spherical, or constant along a radial plane if the outer chamber is not spherical
"rendering uniform"	to make the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument
"Means . . . for rendering uniform the radial absorbed dose profile of the emissions"	Function: Making the absorbed dose of radiation more uniform to prevent over-treatment of body tissue at or close to the outer wall of the instrument. Structure: A radiation absorbing or attenuating material, <i>e.g.</i> , air, x-ray contrast fluid, contrast media used in angiography, water, a gas, or barium sulfate or their equivalents.
"The radioactive material"	The material of claim 1 containing a radionuclide.
"A plurality of radioactive solid particles placed at predetermined locations within the inner spatial volume to provide a desired composite radiation profile"	(no construction needed)
"interstitial"	involving a surgically-created cavity in a body
"brachytherapy"	radiation therapy delivered by a spatially-confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site
"interstitial brachytherapy"	(no construction necessary)


"outer spatial volume"	a region of space defined by an expandable surface element and surrounding an inner "expandable surface element"(no construction needed)
"radiation source"	radionuclide
"minimum prescribed dose"	(no construction necessary)
"delivering a prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"the inner and outer spatial volumes are configured to provide a minimum prescribed absorbed dose"	(no construction necessary)
"a minimum distance outward from the outer spatial volume expandable surface"	(no construction necessary)
"controlled dose"	(no separate construction necessary)
"to reduce or prevent necrosis in healthy tissue proximate to the expandable surface"	(no separate construction necessary)
"providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent necrosis in healthy tissue"	controlling the ratio of the dose at the expandable surface of the outer spatial volume to the prescribed dose at the depth of interest in the target issue so that the dose at the expandable surface is not so high that it lethally damages cells in healthy tissue in contact with the expandable surface
"adapting the expandable surface to contact tissue surrounding the resection cavity to conform the tissue"	(no construction necessary)
"desired shape of the expandable surface element"	(no construction necessary)
"predetermined spacing"	(no construction necessary)
"a predetermined spacing is provided between said inner spatial volume and the expandable surface element" / "a predetermined spacing between said inner spatial volume and the expandable surface element"	the distance between the inner spatial volume and the expandable surface element is determined in advance
"intraoperatively"	following tumor resection, but prior to closing the surgical site
"solid radiation source"	a radionuclide of definite shape and volume; not liquid or gaseous

"the prescribed absorbed dose is delivered to the target tissue in substantially three dimensions"

the prescribed absorbed dose is delivered to the target tissue such that all points at a given outward distance from the tissue wall will receive the same dose

2. The parties shall appear for a further case management conference on June 1, 2007 at 10:30 a.m. and shall file a further joint case management conference statement no later than four days prior.

DATED: 4/27/07


RONALD M. WHYTE
United States District Judge

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10 Counsel are responsible for distributing copies of this document to co-counsel that have not
11 registered for e-filing under the court's CM/ECF program.

12 **Dated:** 4/27/07

13 SPT
14 **Chambers of Judge Whyte**

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION,
and HOLOGIC L.P.,

Plaintiffs,

vs.

SENORX, INC.,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C08 00133 RMW (RS)

**DECLARATION OF LYNN J. VERHEY,
Ph.D. IN SUPPORT OF PLAINTIFFS'
PROPOSED CONSTRUCTION OF CLAIM
TERMS, PHRASES AND CLAUSES**

1 I, Lynn J. Verhey, Ph.D., declare and state as follows:

2 I have been retained in this case as an expert witness by Plaintiffs Hologic, Inc., Cytoc
3 Corporation, and Hologic L.P. (“Hologic”). I make this declaration based on my personal knowledge,
4 training and experience, and if I were to be called to testify, I could and would testify competently
5 about the subject matter set forth below.

6 I understand that the parties propose different constructions of various terms, phrases and
7 clauses in the patents-in-suit. I submit this declaration to provide my opinion on the meaning of the
8 disputed claim terms.

9 **I. INTRODUCTION AND MY EXPERT QUALIFICATIONS**

10 On April 3, 2008, in support of Hologic’s Motion for Preliminary Injunction, I submitted a
11 declaration describing my current employment and summarizing my background and education. Ex. A
12 (¶¶ 3-7) (Dkt. No. 77). I have also submitted a current curriculum vitae to the Court. Ex. B. In the
13 April 3, 2008 declaration, I explained that I previously served as an expert witness for Cytoc
14 Corporation (Cytoc has since been acquired by Hologic) in the case of *Xoft, Inc. v. Cytoc Corporation*
15 *and Proxima Therapeutics, Inc.*, Case No. C05-05312 RMW (¶ 8) (the “Xoft litigation”). The Xoft
16 litigation involved United States Patent Nos. 5,913,813 (the “’813 patent”) and 6,413,204 (the “’204
17 patent”), both of which are at issue in this case.¹ In that declaration, I also briefly described the subject
18 matter of the three patents-in-suit. Ex. A at ¶ 9. Rather than repeating those statements again, I
19 incorporate the contents of my April 3, 2008 declaration by reference.

20 **II. TOPICS THAT I HAVE BEEN ASKED TO ADDRESS**

21 I have been asked to provide opinions regarding how a person of ordinary skill in the art would
22 interpret the meaning of certain claim terms and phrases from the ‘813, ‘204 and ‘142 patents.

23 **III. INFORMATION CONSIDERED IN FORMING MY OPINIONS**

24 On October 12, 2006, I submitted a declaration in the prior Xoft litigation relating to claim
25 construction issues in that case. Ex. C. A substantial part of that declaration is relevant to the present
26

27 ¹ A third patent, United States Patent No. 6,482,142 (the “’142 patent”), is also at issue in this case.
28

1 case. Rather than repeating those statements again, I incorporate the contents of my October 12, 2006
2 declaration by reference. Ex. C. Therein, I identified the information I considered in forming my
3 claim construction opinions. *Id.* at 2-3. I have considered the same information here, with the
4 following additions: (1) I have reviewed and considered the text of the '142 patent and the file history
5 associated with its issuance; (2) I have reviewed and followed the claim constructions that the Court
6 issued in the Xoft case for the '813 and '204 patents; and (3) I have reviewed and considered the claim
7 constructions proposed by the parties in this case. I have not reviewed any written or oral opinions
8 from any expert whom SenoRx has retained or may retain in connection with this case. I reserve the
9 right to modify my opinions stated in this declaration after having reviewed any such opinion offered
10 by any such expert. I also reserve the right to modify my opinions based on any rulings that the Court
11 might issue in the future relating to these patents.

12 **IV. APPROACH I HAVE USED IN READING THE '813, '204, AND '142 PATENTS AND**
13 **INTERPRETING THEIR CLAIMS**

14 In my October 12, 2006 declaration (Ex. C), I explained my methodology for interpreting claim
15 terms and phrases from the '813 and '204 patents. The statements made in that declaration with regard
16 to my approach to claim construction apply equally to the present case.

17 This case involves one additional patent and different asserted claims. I understand that the
18 claims of the '813 patent at issue in this lawsuit are claims 11 and 12, found in columns 5 and 6 of the
19 patent. I understand that the claims of the '204 patent at issue here are claims 4 and 17, found in
20 columns 8 and 9 of the patent. I understand that the claims of the '142 patent at issue here are claims
21 1, 6 and 8, found in columns 8, 9, and 10 of the patent. I understand that all three patents are related to
22 one another by lineage, with the '813 patent being the parent. The '204 and '142 patents are
23 continuations-in-part of the '813 patent.

24 **V. LEVEL OF SKILL OF ONE OF ORDINARY SKILL IN THE ART**

25 In my October 12, 2006 declaration (Ex. C), I identified the skill level of one of ordinary skill
26 in the art for purposes of interpreting the claims of the '813 and '204 patents. *Id.* at 4. The same skill
27 level would apply to construing the '142 patent claims.

VI. THE MEANING OF THE DISPUTED CLAIM TERMS IN THE ‘813, ‘204, AND ‘142 PATENTS

I have reviewed and relied upon the material identified in Section III above. Based on these materials, my knowledge and experience in the technical field to which the patented inventions relate, and my familiarity with the level of ordinary skill in the art at the times the applications for the ‘813, ‘204, and ‘142 patents were filed, I have formed opinions as to how one of ordinary skill in the art would have interpreted certain claim terms at the time of their invention. My opinion regarding the meaning of each of the disputed claim terms is set forth below. Where the disputed term is present in more than one of the asserted patents, my interpretation is given only once. The list of disputed terms includes those identified by either party. For a few of the terms, I provide an explanation of why I disagree with SenoRx’s proposed construction.

VII. TERMS ALREADY CONSTRUED IN THE PRIOR XOFT LITIGATION

I notice that SenoRx disputes a number of claim terms that the Court already construed in the prior Xoft litigation. I will not address those terms already construed by the Court. I reserve the right to address them at a later point in time if appropriate.

The ‘813 Patent

“inner spatial volume” (claims 1, 2, and 12) - The Court previously construed this term to mean “a region of space surrounded by an outer spatial volume and either enclosed by a polymeric film wall or defined by the outside surface of a solid radionuclide.” Col. 1:50-2:3; 2:33-63; 3:9-16, 42-48; 3:64-4:12; 4:16-30, 32-52; 6:6-7; Figs. 1, 3-5; Decl. of Katharine Altemus in Support of Plaintiffs’ Opening Claim Construction Brief (“Altemus Decl.”) at 3-5, 28 (Claim Construction Order from *Xoft, Inc. v. Cytyc Corp. et al.*) I address this term again only to respond to a particular problem I see with SenoRx’s proposed construction.

SenoRx proposes to modify the Court’s construction to limit, for embodiments where the “inner spatial volume” is defined by the outside surface of a solid radionuclide, the radionuclide to a “sphere.” This is an artificially narrow construction, which does not accurately reflect standard brachytherapy treatment. One skilled in the art of brachytherapy would know that in a typical brachytherapy procedure using a solid radionuclide, the radionuclide is not necessarily spherical in

1 shape and does not need to be. This was also true in 1997, when the application for the '813 patent
 2 was filed. Therefore, to so limit the definition of the term "inner spatial volume" does not accurately
 3 reflect standard practice. Nor does it comport with the claim language, which does not include or
 4 imply such limiting language.

5 "inner, closed chamber" (claim 2) – One of ordinary skill in the art would understand this term
 6 as written – i.e., it means "inner, closed chamber." No further elaboration or explanation is needed.

7 It does not make sense from a technical standpoint to say that the inner spatial volume must be
 8 "completely" inside the outer chamber or "closed off within the outer chamber," as SenoRx suggests.
 9 Clearly, as seen in the text of the '813 patent, Col. 2:36-38, and as commonly understood in the field,
 10 an inner spatial volume that is an inner, closed chamber defined by a radiation transparent wall must
 11 still permit a radiation source to be placed in there. If it were completely sealed or closed off, that
 12 would not be possible.

13 **The '204 Patent**

14 "three-dimensional isodose profile that is substantially similar in shape to the expandable
 15 surface element" (claim 1) – means exactly that, "three-dimensional isodose profile that is substantially
 16 similar in shape to the expandable surface element." One of ordinary skill in the art would understand
 17 this term as written. No further elaboration or explanation is needed.

18 "plurality of solid radiation sources" (claim 17) – means exactly that, "plurality of solid
 19 radiation sources." One of ordinary skill in the art would understand this term as written. No further
 20 elaboration or explanation is needed.

21 "isodose profile having a shape substantially similar to the shape of the outer spatial volume"
 22 (claim 17) – means exactly that, "isodose profile having a shape substantially similar to the shape of
 23 the outer spatial volume." One of ordinary skill in the art would understand this term as written. No
 24 further elaboration or explanation is needed.

25 **The '142 Patent**

26 "three-dimensional apparatus volume configured to fill an interstitial void" (claims 1 and 8) –
 27 In my opinion, this claim phrase can only be understood in the context of the limitation in which it
 28

1 appears and is a part of. This limitation is “an expandable outer surface *defining* a three-dimensional
 2 apparatus volume *configured to fill* an interstitial void created by the surgical extraction of diseased
 3 tissue *and define* an inner boundary of the target tissue being treated.” As the italicized language
 4 makes clear, the “three-dimensional apparatus volume” is something that is defined by the “expandable
 5 outer surface.” What this expandable outer surface defines is a three-dimensional geometric solid
 6 (e.g., a sphere) having both volume that fills an interstitial void created by the surgical extraction of
 7 diseased tissue and a surface area that defines an inner boundary of the target tissue being treated.
 8 Accordingly, in my opinion, the term “three-dimensional apparatus volume” means “a three-
 9 dimensional geometric solid composed of an expandable outer surface.” By “solid,” I mean a
 10 geometric shape, such as a sphere, having three dimensions and a surface area.

11 In my opinion, SenoRx construes this claim term divorced from its context. I agree that the
 12 patentee’s use of the word “volume” here is somewhat unusual. However, it is clear from the context
 13 that the patentee uses the term “apparatus volume” to refer to a three-dimensional geometric solid or
 14 shape defined by the expandable outer surface rather than “a region of space within the expandable
 15 outer surface” – as SenoRx’s suggests. Col. 2:20-53, 60-64; 3:20-36, 55-62, 66-67; 4:1-2, 27-42; 5:36-
 16 65; 6:11-29; 8:1-32, 52-59, Figs. 1, 3-4.

17 “located so as to be spaced apart from the apparatus volume” (claim 1) – Like the preceding
 18 claim phrase, this claim phrase can only be understood in the context of the limitation in which it
 19 appears and is a part of. This limitation is “a radiation source disposed completely within the
 20 expandable outer surface and located so as to be spaced apart from the apparatus volume.” As noted
 21 above, the three-dimensional apparatus volume is a geometric solid defined by the expandable outer
 22 surface that has both volume and surface area. Understood in this context, the phrase “located so as to
 23 be spaced apart from the apparatus volume” logically refers to the surface area of the apparatus volume
 24 that defines the inner boundary of the target tissue being treated. Accordingly, in my opinion, this
 25 claim phrase means “located so as to be not on or touching the apparatus volume.” Col. 2:20-53; 3:20-
 26 25, 55-62, 66-67; 4:1-2, 27-30, 35-57; 5:36-65; 6:11-29; 7:1-15, 49-55; 8:1-32, 52-59; Figs. 1, 3-4.

27 \\\

1 "asymmetrically located and arranged within the expandable surface" (claim 1) – means
2 "located and arranged so as not to be on the longitudinal axis of the expandable surface." Col 2:20-53;
3 3:7-19, 55-62, 66-67; 4:1-2; 5:12-37; 6:11-29, 24-67; 7:1-15; 8:1-32, 52-59; Figs. 1, 3-4.

4 "predetermined asymmetric isodose curves" (claims 1, 6 and 8) – means "predetermined
5 isodose curves that are not symmetric with respect to the longitudinal axis of the apparatus volume."
6 Col. 2:20-53; 2:60-3:1; 3:7-19; 5:12-37; 6:11-29, 24-67; 7:28-48; 7:62-8:32; 8:52-59.

7 "plurality of solid radiation sources" (claim 6) – means exactly that, "plurality of solid radiation
8 sources." One of ordinary skill in the art would understand this term as written. No further elaboration
9 or explanation is needed.

10 "being provided on at least two elongate members extending into the apparatus volume" (claim
11 6) – means exactly that, "being provided on at least two elongate members extending into the
12 apparatus volume." One of ordinary skill in the art would understand this term as written. As
13 explained above, the three-dimensional apparatus volume defined by the expandable outer surface is a
14 geometric solid that has both volume and surface area. In the context of this limitation, it is clear the
15 two elongate members are extending into the volume of this geometric solid.

16 I declare that the foregoing is true and correct to the best of my knowledge under penalty of
17 perjury.

18 Executed on May 21, 2008 in San Francisco, California.

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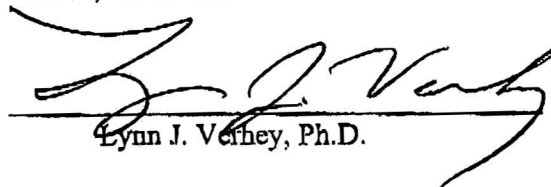

Lynn J. Verhey, Ph.D.

Exhibit A

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION,
and HOLOGIC L.P.,

Plaintiffs,

vs.

SENORX, INC.,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C08 00133 RMW (RS)

**DECLARATION OF LYNN J. VERHEY,
Ph.D. IN SUPPORT OF PLAINTIFFS'
MOTION FOR PRELIMINARY
INJUNCTION**

Date: April 21, 2008

Time: 2:00 p.m

Room: Courtroom 6, 4th Floor

Judge: Hon. Ronald M. Whyte

I, Lynn J. Verhey, Ph.D., declare and state as follows:

1. I have been retained in this case as an expert witness by Plaintiffs Hologic, Inc., Cytac Corporation, and Hologic L.P. I make this declaration based on my personal knowledge, training and experience, and if I were to be called to testify, I could and would testify competently about the subject matter set forth below.

2. I am presently employed by the University of California, San Francisco, as a Full Professor and I serve as Vice-Chair in the Department of Radiation Oncology. Attached to this declaration as Exhibit A is a copy of my curriculum vitae.

3. To briefly summarize my background and education, I received my B.A. in Physics from Kalamazoo College, Kalamazoo, Michigan in 1962, and my M.S. and Ph.D. in Physics in 1964 and 1968, respectively, from the University of Illinois, Urbana, Illinois. The subject of my research during my education was on the decays of certain charged particles produced by high energy interactions of protons with Hydrogen and Deuterium.

4. After earning my doctorate, I took a position at UCLA and served as a post-doctoral researcher and Assistant Professor of Physics from 1968-70, doing experiments at Lawrence Berkeley Laboratory and teaching physics to undergraduate physics students. I then moved to Harvard University in 1970 as an Assistant Professor, continuing to teach undergraduate physics and perform high energy experiments, this time at Fermi National Laboratory in Illinois.

5. In 1975 I took a position as Hospital Radiation Physicist at Massachusetts General Hospital (MGH) with a concurrent continuing position as Assistant Professor at the Harvard Medical School. I then worked with the MGH group to develop and implement proton radiation therapy as an alternative to x-ray therapy.

6. In 1990, I took the position as Chief of the Physics Division and Associate Professor in the Department of Radiation Oncology at UCSF. Since that time, I have continued to serve as Physics Chief and, in addition, as Vice-Chair of the Department and as a Full Professor. As part of my responsibilities at UCSF, I have mentored numerous graduate and post-graduate students, taught graduate classes in the Department of Bioengineering at the University of California, Berkeley as well

1 as at UCSF. I have taught medical physics to medical residents at UCSF as well as to physics
2 residents. I have performed research on methods of delivering radiation to cancer patients and have
3 published over 100 technical papers in this field.

4 7. I was certified as a therapeutic radiological physicist by the American Board of
5 Radiology in 1982, appointed a fellow of the American Association of Physicists in Medicine in 2002
6 and a fellow of the American Society of Therapeutic Radiology and Oncology in 2006. I am a well-
7 recognized expert in methods of delivering radiation to cancer patients, having given numerous
8 scientific lectures and scientific meetings, both nationally and internationally.

9 8. I previously served as an expert witness for Cytoc Corporation in the case of *Xoft, Inc.*
10 *v. Cytoc Corporation and Proxima Therapeutics, Inc.*, Case No. C05-05312 RMW, which was also
11 pending in this Court. I understand that this case, like the *Xoft* case, involves claims of infringement of
12 United States Patent Nos. 5,913,813 (the "813 patent") and 6,413,204 (the "204 patent"). I also
13 understand that a third United States Patent, No. 6,482,142 (the "142 patent"), is involved in this case
14 as well.

15 9. In general, the 813 patent describes and claims an invention in the field of a balloon
16 catheter for treatment of proliferative tissue, while the 204 patent extends this concept to describe and
17 claim as an invention a method for treatment of proliferative tissue diseases using an interstitial
18 brachytherapy apparatus. These patents describe a catheter which can be used with an array of
19 radiation-producing materials to irradiate the wall of a surgical cavity and a defined thickness of tissue
20 beyond that wall, to doses that can both avoid necrosis of normal tissue and destroy cancer cells that
21 might populate the area. The 142 patent further extends the concept of the 813 patent to describe and
22 claim balloon catheter devices that are capable of delivering asymmetrically shaped radiation doses.

23 10. In connection with my role as an expert witness in the *Xoft* case, I offered this Court the
24 following definition of a person of ordinary skill in the art, which is applicable here as well given that
25 the same family of patents is at issue. In understanding what is taught and claimed in the 813, 204 and
26 142 patents, the relevant scientific area is radiation oncology physics, with a focus on brachytherapy.
27 Typically, individuals of ordinary skill in the art of this field would hold an M.S. degree in Physics or
28

Engineering, with 3 or more years of clinical medical physics experience; or a Ph.D. degree in Physics or Medical Physics with 2 or more years of clinical experience.

11. Such a person would have a broad knowledge of the physics of brachytherapy procedures, of the principles of radioactivity and an understanding of the effects of radiation on cells. In addition, such a person would have an understanding of other means of treating cancer cells with radiation such as an external, gantry-mounted linear accelerator. Individuals with such qualifications are considered eligible for certification as a radiation oncology physicist by entities such as the American Board of Radiology and considered capable of working independently in a clinical environment as a medical physicist.

12. I have been asked by Plaintiffs' counsel to describe, from the viewpoint of a person of ordinary skill in the art (as defined above), what is disclosed and taught in two technical documents: (1) a 1990 article entitled "A New Technique of Brachytherapy for Malignant Gliomas with Cesium-137: A New Method Utilizing a remote Afterloading System," by Ashpole et al. (attached as Ex. 5 to the Declaration of Aaron P. Maurer) ("Ashpole"), and (2) U.S. Patent No. 5,931,774 to Williams, et al. (attached as Ex. 13 to the Declaration of Aaron P. Maurer) (the "774 patent"), entitled "Inflatable Devices for Tumor Treatment" which describes "implantable devices for treatment of proliferative disorders." I have been provided with copies of both documents and have reviewed them.

13. Ashpole describes the irradiation of a cavity from which a brain tumor has been removed, using an intracranial applicator made by modifying an endotracheal tube. In its unmodified form, the endotracheal tube has an open lumen that provides an unobstructed airway and an inflatable balloon, called a cuff, attached near its distal end that seals the space between the tube and the trachea to prevent the aspiration of unwanted matter from the pharynx into the trachea. To be used as an intracranial applicator, the endotracheal tube is shortened in length and sealed off at its distal end, just beyond the lower end of the balloon. Page 334, column 1.

14. The intracranial applicator is visually inserted into the postsurgical cavity following the removal of the brain tumor, and the balloon is then inflated with a radio-opaque fluid (needed for treatment planning purposes) so that it approximately fills the cavity. The volume of fluid used varies

column 2.

15. There is no teaching in Ashpole that the balloon can be expanded to conform the shape of the cavity to the outer surface of the balloon, or that the balloon comes into contact with the tumor bed at all points, or that the distance from the tumor bed to the radiation source can be adjusted through expansion of the balloon. Indeed, one of ordinary skill in the art would understand that undue deformation and compression of sensitive normal brain tissue caused by the influx of an incompressible fluid, are not desirable.

16. After the intracranial applicator has been implanted, it is attached to a Selectron remote afterloader, which pushes dummy sources into the tube, using positions which represent potential dwelling points for the radioactive sources during treatment. Ashpole produces a desired mean dose rate at a given distance from the balloon's surface by varying the position of active and inactive beads in the source train until an isodose curve is found, which is a satisfactory match to the cavity shape. In other words, the desired dose distribution is a direct result of the particular arrangement of active and inactive beads on a source train, and Ashpole aims to compute an isodose surface that conforms to the particular shape of the postsurgical cavity, rather than reshaping the cavity to conform to the outer surface of the balloon. Page 336, column 1 ("A certain measure of dosimetrical versatility is possible in that the positions of the active beads can be changed to produce an isodose distribution specific to the geometry of the individual tumor beds.").

17. In Ashpole the configuration of the balloon plays a role only to ensure that the dose at the prescribed depth of 0.5 cm is greater than 50% of that at the surface of the balloon. To ensure the minimum ratio, Ashpole teaches that "the balloon diameter should not be less than 2.5 cm." Page 336, column 2. Ashpole does not teach changing the balloon diameter after implantation. Rather, it prescribes a minimum diameter to which a balloon should be inflated with radio-opaque fluid during implantation.

18. Ashpole does not disclose controlling the dose at the surface of the balloon so that it is not so high that it lethally damages healthy brain cells in contact with the surface. For instance, it

1 indicates that "[t]he dose at the surface of the balloon . . . can be as high as 70 Gy," notwithstanding
2 the fact that "the limited tolerance of normal brain has restricted the maximum permissible dose to
3 about 55-60 Gy." Page 333, column 2; page 336, column 2. Furthermore, if one applies the inverse
4 square law to Ashpole's "typical case [of] a balloon diameter of 2.9 cm," then a depth dose of 50Gy at
5 0.5 cm from the surface of the balloon would mean a dose of approximately 90 Gy at the surface,
6 assuming a symmetric distribution of sources within the balloon. Ashpole's teaching of a minimum
7 balloon diameter of 2.5 cm suggests that for a dose of 50Gy at 0.5 cm from the cavity surfact, that the
8 dose at the surface can be even higher than 90 Gy.

9 19. Ashpole explains that the intracranial applicator avoids the problem of late or delayed
10 radionecrosis observed with the use of long-term wire implants because the intracranial applicator is
11 removable and implanted into an area from which the tumor has already been debulked. Page 336,
12 column 2.

13 20. The 774 patent discloses an implantable balloon applicator for delivering one or more
14 treatment fluids to target tissue. Although it discusses several embodiments, the one of particular
15 interest is a "double balloon device" with an outer and inner balloon, as depicted in Figure 3.

16 21. The 774 patent teaches that "it is preferable that the balloon have a shape that permits
17 the balloon to conform to the body cavity or lumen in which the balloon is to be inflated." Column 7,
18 lines 41-43. Furthermore, "[i]n certain embodiments, a balloon will be selected such that, upon
19 inflation, the balloon does not compress the tissue which is being treated, or surrounding tissues. Thus,
20 when a radioactive treatment fluid is introduced into the device, e.g., by injection, the treatment device
21 is inflated to a volume not substantially greater than a volume of the body cavity in which the device
22 has been placed, thereby avoiding any substantial compression or distortion of normal tissue." Column
23 7, lines 48-56. This is consistent with the disclosure in Ashpole, in which the applicator balloon,
24 because it is being used within the brain, is inflated with fluid to a volume only sufficient to fill the
25 postsurgical cavity in which the device has been placed but not to cause any compression or
26 deformation of the surrounding brain tissue.

22. The double balloon device of Figure 3 is shown as having two treatment fluid receptacles, one in communication with the outer balloon and the other one in communication with the inner balloon. Column 8, lines 41-46 and 54-60. The outer balloon in this example is filled with a chemotherapeutic fluid and the inner balloon is filled with a radioactive fluid. Column 8, lines 60-65.

23. Although Figure 3 shows the inner balloon as having an off-center position relative to the outer balloon, this is a schematic view only and not something drawn to scale. Column 3, lines 1-2. Accordingly, the degree to which the inner balloon occupies an asymmetric position relative to the outer balloon, which is not mentioned or discussed at all in the 774 patent, cannot be determined. It would depend on the device's actual design and construction.

24. More importantly, neither Figure 3 nor the specification of the 774 patent teaches a person of ordinary skill in the art how the radiation source in the inner balloon can be *located and arranged* to provide *predetermined* asymmetric isodose curves relative to the outer balloon. If the inner balloon has an asymmetry relative to the outer balloon, that asymmetry is fixed by the geometric constraints of the device, and therefore the position of the inner balloon cannot be altered to provide predetermined asymmetric isodose. Instead, any asymmetric dose distribution produced by the radioactive fluid in the inner balloon would be a byproduct of the inner balloon's inherent asymmetry.

25. In addition to the *Xoft* case mentioned above, for which I provided both deposition and hearing testimony, I provided testimony as an expert at a deposition in the case of *Maggiani vs. University of Southern California* conducted on February 20, 2006.

26. I am being compensated for my work on this matter at a rate of \$500 per hour. My compensation does not depend on the outcome of this case.

I declare that the foregoing is true and correct to the best of my knowledge under penalty of perjury.

Executed on April 3, 2008 in San Francisco, California.

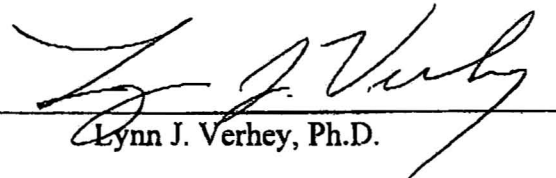

Lynn J. Verhey, Ph.D.

Exhibit B

Lynn J. Verhey, PhD

University of California, San Francisco

Updated: 5/10/07

CURRICULUM VITAE

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FAX: (415) 353-7182

email: verhey@radonc17.ucsf.edu

EDUCATION:

1958-62	Kalamazoo College, Kalamazoo, MI	BA	Physics, Cum Laude
1962-64	University of Illinois, Urbana, IL	MS	Physics
1964-67	University of Illinois, Urbana, IL	PhD	Physics

BOARD CERTIFICATION:

1982	American Board of Radiology (Therapeutic Radiological Physics)
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PRINCIPAL POSITIONS HELD:

1967-70	University of California, LA	Assistant Professor	Physics
1971-72	Harvard University	Lecturer	Physics
1972-75	Harvard University	Assistant Professor	Physics
1975-90	Harvard Medical School	Assistant Professor	Radiation Therapy
1991-96	University of California, SF	Assoc. Professor in Residence	Radiation Oncology
1996-now	University of California, SF	Professor in Residence	Radiation Oncology

OTHER POSITIONS HELD CONCURRENTLY:

1975-78	Massachusetts General Hospital	Assistant Biophysicist	Radiation Medicine
1978-90	Massachusetts General Hospital	Associate Biophysicist	Radiation Medicine
1978-90	Massachusetts General Hospital	Head, Clinical Physics	Proton Therapy

1991-now	University of California, SF	Chief of Physics	Radiation Oncology
1991-now	University of California, SF	Vice-Chair	Radiation Oncology
1991-00	University of California, SF	Faculty	Graduate Group in Biophysics
1994-now	UCSF and UC Berkeley	Faculty	Bioengineering Graduate Group

HONORS AND AWARDS:

1962	Phi Beta Kappa, Kalamazoo College
1962	John Wesley Hornbeck Prize in Physics, Kalamazoo College, Kalamazoo, MI
2002	Fellow, American Association of Physicists in Medicine
2006	Fellow, American Society of Therapeutic Radiation and Oncology

KEYWORDS/AREAS OF INTEREST:

Radiotherapy, intensity modulation, protons, radiosurgery, ocular melanoma, dosimetry, image-guided radiotherapy, magnetic resonance spectroscopy, cancer of the prostate, head and neck and brain.

PROFESSIONAL ACTIVITIES

CLINICAL:

Head of clinical physics from 1978-90 for the proton radiation treatment program of the Department of Radiation Therapy, Massachusetts General Hospital.

Director of Physics for Gamma Knife Facility, University of California, San Francisco since 1991

Director of Physics for ocular melanoma proton treatment facility University of California, San Francisco and University of California, Davis since 1994

Implementation and direction of intensity modulated radiotherapy treatments at UCSF since 1997

Specification and oversight for acquisition, installation, commissioning and operation of \$20 million state-of-the-art Radiation Oncology Department at UCSF Comprehensive Cancer Center at Mount Zion from 1998 to present

SUMMARY OF CLINICAL ACTIVITIES

As Chief of Physics in the Department of Radiation Oncology at UCSF, I am responsible for all technical aspects of the planning and delivery of sophisticated precision radiotherapy and radiosurgery. This includes supervision and oversight of approximately 20 radiation therapists, six dosimetrists, two engineers and eight physicists. I provide oversight and direction to the physics faculty in their clinical service and in the development of new clinical delivery schemes and imaging methods. As Director of Physics for the Gamma Knife, I coordinate and oversee quality assurance of treatments, safety and radiation training of all personnel, new upgrades of software and hardware and the installation of new radiation sources.

PROFESSIONAL ORGANIZATIONS:Memberships

1962	Phi Beta Kappa
1966	Sigma Pi Sigma
1975-80	American Association of Physics Teachers
1976-now	American Association of Physicists in Medicine
1979-now	American Society of Therapeutic Radiologists
1979-99	Radiation Research Society
1983-90	American Association for the Advancement of Science
1984-now	Proton Therapy Cooperative Group
1986-90	New York Academy of Science
1992-now	International Stereotactic Radiosurgery Society
1995-now	California Radiological Society
1995-now	American College of Radiology

Service to Professional Organizations

1991-97	Chairman of Quality Assurance Committee of Proton Radiation Oncology Group Sponsored by American College of Radiology
1992-99	Member, RTOG Committee on Quality Assurance in Conformal Radiation Therapy (3D-CRT)
1992-97	Member, Radiation Physics Committee of American Society for Therapeutic Radiology and Oncology (ASTRO)
1992-93	Member, Research Committee, American Association of Physicists in Medicine (AAPM)
1993-95	Reviewer for Awards and Honors Committee of AAPM
1993-now	Reviewer of abstracts for Annual meeting of AAPM
1993-03	Reviewer of abstracts for Annual Meeting of ASTRO
1994	Reviewer of abstracts for 1994 Annual Meeting of the Radiological Society of North America (RSNA)
1995-now	Member, Committee on Quality Assurance for Cooperative Clinical Trials, a Subcommittee of the Radiation Therapy Committee of the AAPM
1996-01	Member, Committee on Membership of ASTRO
1996-01	Member, 3D Committee of the Radiation Therapy Oncology Group (RTOG)
2000-02	Member, Awards Committee of ASTRO
2003-now	Member, Corporate Working Group of ASTRO

SERVICE TO PROFESSIONAL PUBLICATIONS

1998-now	Editorial Board, International Journal Radiation Oncology, Biology and Physics (IJROBP)
1988-now	Ad hoc referee for IJROBP (10 papers in past 5 years), Medical Physics (5 papers in past 5 years), British Journal of Radiology (2 papers in past 5 years), Radiotherapy and Oncology (2 papers in past 5 years), Physics in Medicine and Biology (8 papers in past 5 years)

INVITED PRESENTATIONS (PAST 15 YEARS)**INTERNATIONAL**

1991 International Workshop on Heavy Charged Particle Therapy and Related Subjects, National Institute for Radiological Sciences, Chiba, Japan

1991 World Congress on Medical Physics and Biomedical Engineering, Kyoto, Japan

1993 International Leksell Gamma Knife Society Meeting, Aronsborg, Sweden

1993 International Symposium on 3D Radiation Treatment Planning and Conformal Therapy, St. Louis, MO

1994 Proton Therapy Cooperative Group Meeting, Chester, England

1994 Proton Therapy Cooperative Group Meeting, Chiba, Japan

1995 Siemens Vision Group on New Directions in Radiotherapy, Frankfurt, Germany

1995 Annual Meeting of the International Commission on Radiation Units and Measurements (ICRU) in Remscheid-Lennep, Germany

1995 US-Japan Radiation Oncology Meeting, San Francisco, CA

1995 International Stereotactic Radiosurgery Meeting, Boston, MA

1997 XII International Conference on the Use of Computers in Radiation Therapy, Salt Lake City, Utah

1997 First Professor S. Takahashi Memorial International Workshop on Three Dimensional Conformal Radiotherapy, Nagoya, Japan

1997 Siemens Therapy Products Enduser Meeting and Seminar, Beijing, China

1997 International Congress of Radiation Oncology, Beijing, China

1997 Third Congress of the International Stereotactic Radiosurgery Society, Madrid, Spain

1997 ESTRO Workshop on Challenges in Conformal Radiotherapy, Nice, France

1998 DKFZ (Deutsche Krebs Forschung Zentrum), Heidelberg, Germany

1998 3rd International Symposium on 3-D Radiation Treatment Planning and Conformal Radiotherapy, Chapel Hill, NC

1998 Second Professor S. Takahashi Memorial International Workshop on Three Dimensional Conformal Radiotherapy, Nagoya, Japan

1999 International Stereotactic Radiosurgery Society (ISRS) Meeting, Sydney, Australia

1999 Annual Meeting of Societe Francaise De Radiotherapie Oncologique, Paris, France

2000 2nd Annual Wharton Lecture, Princess Margaret Hospital, Toronto, Canada

2000 Hallym Hospital, Seoul, Korea

2000 Samsung Hospital, Seoul, Korea

2000 Addenbrookes Hospital, Cambridge, England

2000 Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO), Istanbul, Turkey

2000 First International Symposium on Stereotactically Guided IMRS/IMRT, Los Angeles, CA

2001 International Congress on Radiation Oncology (ICRO), Melbourne, Australia

2001 Sun-Yat-Sen Cancer Center, Taipei, Taiwan

2001 Third Professor S. Takahashi Memorial International Workshop on Three Dimensional Conformal Radiotherapy, Nagoya, Japan

2002 Leksell Gamma Knife Society Meeting, Prague, Czech Republic

2002 Hospital Sirio Libanes, Sao Paulo, Brazil

- 2002 Joint Meeting Canadian Organization of Medical Physicists and American Association of Medical Physicists, Montreal, Canada
- 2003 NZIMRT Annual Conference, Hamilton, New Zealand
- 2003 Organizer, Moderator and Speaker, 7th International Conference on 3DCRT/IMRT, San Francisco, CA
- 2003 2nd International Conference on Translational Research and Pre-Clinical Strategies in Radio-Oncology, Lugano, Switzerland
- 2004 Fourth Professor S. Takahashi Memorial International Workshop on Three Dimensional Conformal Radiotherapy, Nagoya, Japan

NATIONAL

- 1992 Special Focus Panel at Annual Meeting of Radiological Society of North America, Chicago, IL:
- 1993 Special Panel on Conformal Therapy at the Annual Meeting of the American Society for Therapeutic Radiation and Oncology, New Orleans, LA
- 1994 Preuss Foundation Seminar on Stereotactic Radiation Treatment of Brain Tumors, Boston MA
- 1995 Special Workshop at the Annual Meeting of the Radiation Research Society on "New Methods of Delivering Radiation Therapy", San Jose, CA
- 1995 Symposium on Implementation of Emergent Technology in Radiation Oncology, Indian Wells, CA
- 1995 Scientific Session of the Radiation Therapy Oncology Group Annual Meeting, Philadelphia, PA
- 1996 Workshop on Intensity Modulated Radiation Therapy, Durango, CO
- 1996 Radiation Therapy Oncology Group Annual Meeting, Washington, DC
- 1997 Visiting Professor, Duke University Medical Center, Department of Radiation Oncology Grand Rounds, Durham, NC
- 1997 14th Annual Meeting of the American College of Medical Physics, Lake Tahoe, CA
- 1998 20th Annual Engineering Industrial Liaison Program, University of Calif., Berkeley, CA
- 1998 Intensity Modulated Radiation Therapy Workshop, Williamsburg, VA
- 1998 Annual Meeting of the American Association of Physicists in Medicine (AAPM), San Antonio, TX
- 1999 Radiation Therapy Oncology Group (RTOG) Annual Meeting, Atlanta, GA
- 1999 3-D Meeting on Conformal and Intensity Modulated Radiation Therapy, Houston, TX
- 1999 Annual Meeting of AAPM, Nashville, TN
- 1999 National Cancer Institute Workshop on Medical Physics for Clinical Radiotherapy, Washington, DC
- 1999 Annual Meeting of the American Association of Therapeutic Radiology and Oncology (ASTRO), San Antonio, TX
- 2000 3-D Conformal Radiotherapy Workshop, New York, NY
- 2000 Combined Meeting of World Congress of Medical Physicists and AAPM, Chicago, IL
- 2000 Annual Meeting of ASTRO, Boston, MA
- 2000 Siemens Users' Meeting, Kiawah Island, SC
- 2001 International Stereotactic Radiosurgery Society (ISRS), Las Vegas, NM
- 2001 Annual Meeting of AAPM, Salt Lake City, UT

- 2001 Visiting Professor, Symposium Honoring the Career of Dr. Michael Goitein at
Massachusetts General Hospital, Boston, MA
- 2002 Visiting Professor, Department of Radiation Oncology, University of Pennsylvania,
Philadelphia, PA
- 2002 Annual Meeting of ASTRO, New Orleans, LA
- 2003 Annual Meeting of ASTRO, Salt Lake City, UT
- 2003 Organizer, Moderator and Speaker, Proton Therapy Cooperative Group Meeting, San
Francisco, CA
- 2003 Siemens Users' Meeting, Salt Lake City, UT
- 2004 Annual Meeting of AAPM, Pittsburgh, PA
- 2004 Annual Meeting of ASTRO, Atlanta, GA
- 2004 Annual Meeting of American Association of Physics Teachers, Sacramento, CA

REGIONAL AND OTHER INVITED PRESENTATIONS

- 1991 Cancer Education Session, Stanford University Department of Radiation Oncology,
Stanford, CA
- 1993 Department of Physics, Sonoma State University, Rohnert Park, CA
- 1993 Bay Area Chapter of the American Association of Neuroscience Nurses
- 1994 Grand Rounds, Department of Radiation Oncology, UCSF
- 1994 29th Annual San Francisco Cancer Symposium, San Francisco, CA
- 1995 15th Annual Current Approaches to Radiation Oncology, Biology and Physics, San
Francisco, CA
- 1996 Northern California Society of Radiation Therapy Technologists, Concord, CA
- 1997 16th Annual Current Approaches to Radiation Oncology, Biology and Physics, San
Francisco, CA
- 1997 Annual Retreat of the Graduate Group in Biophysics, UCSF, Tiburon, CA
- 1998 17th Annual Current Approaches to Radiation Oncology, Biology and Physics, San
Francisco, CA
- 1999 18th Annual Current Approaches to Radiation Oncology, Biology and Physics, San
Francisco, CA
- 1999 First Annual Radiosurgery Symposium, UCSF
- 2001 Stanford University IMRT Symposium, Palo Alto, CA
- 2002 Cyberknife Users' Meeting, Napa, CA
- 2002 Siemens Users' Meeting, Santa Rosa, CA
- 2002 UCSF-Stanford Post-Graduate Course – Scientific Program Coordinator and Moderator
- 2002 Joint Meeting of SFSU-UCSF U56 Collaborative Advisory Committee
- 2003 UCSF-Stanford Post-Graduate Course – Scientific Program Coordinator and Moderator

GOVERNMENT AND OTHER PROFESSIONAL SERVICE:

- 1990-97 Chair, Report Committee on Proton Therapy, International Commission on Radiation
Units and Measurements (ICRU)
- 1990-91 Loma Linda University Medical Center: Safety Review Committee on the Proton
Therapy Facility
- 1992-93 Lawrence Berkeley Laboratory, University of California, Berkeley: Dosimetry Review
Committee for Heavy Ion Radiotherapy Program

1992 Lawrence Berkeley Laboratory, University of California, Berkeley: Research Medicine and Radiation Biophysics Division Review Committee

1992-93 National Cancer Institute: Program Project Scientific Review Panel

1993 National Cancer Institute: Review Committee for Radiological Physics Center at M.D. Anderson Hospital, Houston, TX

1993-95 Nuclear Regulatory Commission and Lawrence Livermore National Laboratory: Reviewer of Quality Management Plans

1995 TRIUMF and the British Columbia Cancer Agency: Safety Review Committee on the Proton Therapy Facility

1996 National Cancer Institute: Member, Special Review Committee for Program Project at University of Michigan Medical Center

1997-04 Takahashi International Workshop Organizing Committee, Nagoya, Japan

1997-01 National Cancer Institute: Member, Special Ad Hoc Review Committee of the Radiation Studies Section of NCI

1999 External Physics Consultant to Swedish Hospital, Seattle, WA

1999 External Advisor to University of Texas Medical Branch, Galveston, TX

1999-01 National Cancer Institute: Member, Intensity Modulated Radiotherapy Cooperative Working Group

2000 National Cancer Institute: Member, Special Review Committee for Program Project at University of Michigan Medical Center

2000-03 Cancer Research Coordinating Committee of State of California: Reviewer of Research Proposals

2001 Special Advisor to Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Canada

2004 Special Ad Hoc Reviewer of Research Proposal for the Dutch Cancer Society

UNIVERSITY AND PUBLIC SERVICE

UNIVERSITY SERVICE:

UCSF, UC BERKELEY AND UC DAVIS CAMPUS-WIDE

1991-00	Faculty member of the Graduate Group in Biophysics, University of California, San Francisco
1991-93	Member, University of California, Davis Cancer Center Proton Beam Task Force and Clinical Specifications Subcommittee
1992-03	Chair, Radiation Drug Research Committee, University of California, San Francisco
1992-03	Member, Radiation Safety Committee, University of California, San Francisco
1993-95	Member, Environmental Health and Sciences Advisory Group, University of California, San Francisco
1994	Chair, Ad Hoc Promotion Review Committee, University of California, San Francisco
1994	Founding Member, UCSF Cancer Center
1994-now	Faculty member of Bioengineering Graduate Program, University of California, Berkeley
1997-00	Member, Health and Safety Policy Board of the University of California, San Francisco
1998,99,02	Member Ad Hoc Promotion Review Committees, University of California, San Francisco
1998	Vice-Chair, Admissions Committee of the Bioengineering Graduate Program, University of California, Berkeley
1998-now	Specification and oversight for acquisition, installation, commissioning and operation of \$20 M state-of-the-art Radiation Oncology Department at UCSF Comprehensive Cancer Center at Mount Zion
1999	Chair, Admissions Committee of the Bioengineering Graduate Program, University of California, Berkeley
2000-03	Member, Graduate Council of the Academic Senate, University of California, San Francisco
2001-now	Member, UCSF Health and Safety Policy Board
2001-03	Member, Bioengineering Graduate Group Executive Committee
2001-02	Member, Academic Senate Subcommittee on Creation of a UCSF School of Advanced Health Studies
2003-now	Member, Bioengineering Graduate Group Advisors' Committee
2002-03	Service on Qualifying and Final Exam Committees for Bioengineering Grad. Students
2004-	Member, Educational Policy Committee of the Academic Senate, UCSF

DEPARTMENTAL SERVICE

1991-now	Vice Chair and Chief of Physics
1991-now	Member, Internal Computer Committee
1991-now	Member, External Computer Committee
1991-now	Member, Program Committee of Annual Course on Current Approaches to Radiation Oncology, Biology and Physics

1991-94	Member, Mt. Zion -University of California, San Francisco Radiation Oncology Integration Committee
1991-now	Member, Quality Assurance / Quality Improvement Committee
1991-now	Member, Radiation Oncology Research Allocation Committee
1991-now	Member, Radiation Oncology Resident Selection Committee
1991-now	Member, Executive Committee of Department of Radiation Oncology
1993-94	Chair, Faculty Search Committee for Physics Faculty in Hyperthermia
1993-now	Initiator and Director, Physics Residency Training Program in Therapeutic Radiation Oncology Physics
1996	Member, Faculty Search Committee for Assistant Professor in Residence with Combined Research/Clinical Duties
1997	Chair, Ad Hoc Committee for Selection of NOMOS Medical Research Fellow for Clinical Implementation of Intensity Modulated Radiation Therapy
1997	Member, Faculty Search Committee for Wun-Kon Fu Endowed Chair in Radiation Oncology
1998	Member, Senior Promotions Committee
1998	Chair, Ad Hoc Committee for Selection of Siemens Medical Research Fellow
1998	Chair, Faculty Search Committee for Assistant Professor in Residence (Physics)
2001-now	Member, Radiation Oncology Animal Care Review Committee

PUBLIC SERVICE:

1990	Member of scientific delegation for US-Soviet Union Proton Therapy Exchange Program
1993-98	Member, Medical Physics Advisory Committee (MEDPAC), Lawrence Livermore National Laboratory
1998	Scientific American Interview with W. Wayt Gibbs
1998	Wired Magazine Interview with Heidi Kriz
2000-03	Scientific Advisory Board, Accuray, Inc.
2001-04	Scientific Advisory Board, MED-TEC, Inc.

SUMMARY OF SERVICE ACTIVITIES

Most of my service activities in the past five years have been associated with administrative duties within the Department of Radiation Oncology, campus-wide committees, and activities within the cross-campus Bioengineering Graduate Group, where I am an active faculty member. As a member of the executive committee of the Department of Radiation Oncology, I am involved in all decisions relating to finances, promotions and salaries, and space allocation. As the Chief of the Physics Division within the department, I have special mentoring and advising duties for the other physics faculty as well as technical supervision of engineers, dosimetrists and radiation therapists. As Director of the Physics Residency Training Program, I have major responsibilities to select, mentor and advise the residents in their clinical training program. As a member of the Medical Residency Selection Committee, I work with a small group of department faculty to interview and rank resident candidates. As a member of the Program Committee of the Annual UCSF-Stanford Post-Graduate Course on Current Approaches to Radiation Oncology, Biology and Physics, I am responsible for planning and arranging the physics and technical presentations. As a long-standing member of the Radiation

Lynn J. Verhey, PhD

Safety Committee of the campus until 2003, I was one of several members responsible for investigating and analyzing the use of radioactivity in research and in clinical activities. As a member of the Scientific Advisory Board of two vendors of medical equipment used in Radiation Oncology, I have been able to influence the development of devices that improve the quality of patient care.

TEACHING and MENTORING**FORMAL SCHEDULED CLASSES FOR UCSF AND UCB STUDENTS:**

Qtr	Acad. Yr	Course No. & Title	Contribution	Units	Class Size
F,W	1998-99	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F,W	1999-00	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F,W	2000-01	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F,W	2001-02	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F,W	2002-03	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F,W	2003-04	Medicine 424 Therapeutic Radiological Physics	Lecturer	1	5
F	2000-01	NE 167 Engineering Aspects Nuc Med / RadioTherapy	Course Design and Lecturer	3	10
S	2001-02	Bioeng. 230C Physics of Radiation Oncology	Course Design and Lecturer	3	5
S	2003-04	Bioeng 230C Physics of Radiation Oncology	Course Design and Lecturer	3	8
S	2005-06	Bioeng 230C Physics of Radiation Oncology	Course Design and Lecturer	3	4

POSTGRADUATE AND OTHER COURSES

2003 7th International Conference on 3DCRT/IMRT, San Francisco, Organizer, Moderator and Speaker

2002-05 UCSF-Stanford Post-Graduate Course on Radiation Oncology – Scientific Program Coordinator, Moderator and Speaker

2002-06 Gamma Knife Model C training for outside clinicians and physicists

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Program or School	Role	Current Position
1998-99	Nkiruka Emeagwali	Johns Hopkins	Research advisor	Graduate Student
1998-00	Gordon Wong	Bioengineering, UCB	Research advisor	Graduate Student
1999-02	Ted Graves	Bioengineering, UCSF	Research co-mentor	Asst. Prof. Stanford

Lynn J. Verhey, PhD

2000	Andrew Hwang	Bioengineering, UCSF	Rotation coordinator	Graduate Student
2001-02	Richard Cardenas	Texas Tech University	Research co-mentor	Asst Prof St. Marys TX
2003-	Michael Lometti	SFSU MS student	Research co-mentor	Research Associate
2004-	Erica Ludlam	Bioengineering, UCSF	Research co-mentor	Graduate Student
2003-	Olivier Morin	Bioengineering, UCSF	Research co-mentor Academic advisor	Graduate Student
2002-04	Annette A. Chan	Bioengineering, UCSF	Research co-mentor Academic advisor	Post-doctoral Researcher
2004-	Cornelius VonMorze	Bioengineering, UCSF	Academic advisor	Graduate Student

POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED OR MENTORED

Dates	Name	Fellow/Resident	Faculty Role	Current Position
1992-95	Su-Min Zhou	Physics Res. Fellow	Research Advisor	Assoc. Prof. Duke
1993-95	Bruce Hill	Physics Resident	Clinical Training	Physicist - Stanford
1994-95	Tibor Major	IAEA Physics Fellow	Research Advisor	Physicist – Hungary
1994-98	Inder Daftari	Hospital Physicist	Clinical Training	Hospital Physicist UCSF
1994-96	Greg Bednarz	Physics Resident	Clinical Training	Physicist– U. Penn
1995-97	Ping Xia	Physics Resident	Clinical Training	Assoc. Prof. UCSF
1998-00	Michelle Svatos	Physics Res. Fellow	Research Advisor	Physicist - Siemens
1996-98	Jenny Hai	Physics Resident	Clinical Training	Physicist- Stanford
1997-99	D Jay Wiczorek	Physics Resident	Clinical Training	Physicist – Baptist Hosp. Miami
1998-00	Lei Wang	Physics Resident	Clinical Training	Asst Prof Sequoia Hosp
1999-02	Cynthia Chuang	Physics Resident	Clinical Training	Clin. Instructor UCSF
1999-01	Andrea Pirzkall	Research Fellow	Research Supervision	Asst. Adj. Prof. UCSF
2000-03	Katja Langen	Physics Resident	Clinical Training	Physicist – MD Anderson Orlando
2000-01	Khalil Sultanem	Clinical Fellow	Research Supervision	Attending Physician
2002-04	Jose-Eduardo Villarreal	Physics Resident	Clinical Training	Physicist - Mount Diablo Hospital
2001-02	Jean Nakamura	Rad. Onc. Resident	Research Supervision	Instructor, UCSF
2002-05	Ningsheng Zhu	Physics Resident	Clinical Training	Physics Resident
2003-07	Josephine Chen	Research Fellow and Physics Resident	Research and Clinical Training	Research Fellow and Resident

2003-05	Hong Chen	Physics Resident	Clinical Training	Physics Resident
2005-07	Martina Descovich	Physics Resident	Clinical Training	Physics Resident
2007-09	Tarek Halabi	Physics Resident	Clinical Training	Physics Resident

RADIATION ONCOLOGY RESIDENTS AND FELLOWS – CLINICAL INSTRUCTION

1989-92	Marquez, Carol Bahary, Jean-Paul Uhl, Valerie Stalpers, Lucas Feehan, Patrick Gotkowitz, Carrie	Levin, Ken Garwood, Dan Miyawaki, Lloyd Eng, Tony Lillis, Patricia Chang, Garrick	Stalpers, Lucas Levine, Rene Schoenthaler, Robin Scharfen, Cindy Weil, Michael Hunter, Darryl
1992-95	Holland, John Goldsmith, Brian Diaz, Aidnag	Yates, Barbara Schrieve, Dennis Tran, Loan	Maloney, Alan Ling, Stella Schultz, Marion
1995-99	Crownover, Richard Haas-Kogan, Daphne Chou, Rachel Le, Quynh-Thu	Bermudez, Maria-Amelia Bauman, Glenn Chen, Anita Forstner, Julie	Koeplin, David Coleman, Lori Shu, Hui-Kuo Song, Joseph
1999-01	Seung, Steven Posner, Marc	Coleman, Cardella Gottschalk, Alex	Seaward, Samantha Hoffman, Rex
2001-03	Suplica, Jeffrey Fisch, Ben Sultanem, Khalil Nakamura, Jean Lee	Vigneault, Eric Lee, Terry Young, C. Dale Takamiya, Robert	Bertucio, Clare Tsao, May Biggs, Christopher Lowther, David
2003-present	Stickney, Eric Ho, Linh Missett, Brian Chen, Allen Lee, Brian	Doyle, Kelly Huang, David Coleman, Joy Dai, Charlotte	Huang, Kim Rembert, James Millender, Laura Hansen, Eric

INFORMAL TEACHING:

1991-07 Teaching Gamma Knife planning to residents, fellows and faculty
1991-07 In-service lectures on radiosurgery, IMRT and clinical physics

FACULTY MENTORING

Dates	Name	Position while Mentored	Mentoring Role	Current Position
1994-96	Paula Petti	Asst. Professor	Academic and research advisor	Adjunct Professor UCSF
1998-02	Ping Xia	Clinical Instructor	Academic and research advisor, reviewed grant proposal	Associate Professor in Residence, UCSF
2002-now	Cynthia Chuang	Clinical Instructor	Academic and research advisor	Asst. Adjunct Professor, UCSF
2003	Bruce Faddegon	Associate Professor	Reviewed grant proposal	Associate Professor, UCSF
2001-04	Andrea Pirzkall	Assistant Researcher	Reviewed manuscripts, academic advisor	Associate Professor, UCSF
2006-07	Lijun Ma	Associate Professor	Reviewed manuscripts and mentored research	Associate Professor, UCSF

SUMMARY OF TEACHING HOURS:

2002-03 305 total hours of teaching (including preparation)
 Formal class or course teaching hours: 25 hours
 Informal teaching hours: 250 hours
 Mentoring: 30 hours

2003-04 390 total hours of teaching (including preparation)
 Formal class or course teaching hours: 80 hours
 Informal teaching hours: 280 hours
 Mentoring: 30 hours

2004-05 335 total hours of teaching (including preparation)
 Formal class or course teaching hours: 30 hours
 Informal teaching hours: 280 hours
 Mentoring: 25 hours

TEACHING NARRATIVE:

My teaching hours are divided between formal courses, including a quarter course (Bioengineering 230C) recently introduced by me to offer the Physics of Radiation Oncology as a subject. From this course, several graduate students have become interested in research in the physics of Radiation Oncology and are now doing rotations or beginning thesis research in our group. As director of the Physics Residency Training Program, I have been responsible for designing the curriculum, selecting the residents and assuring their progress through the clinical training. Two of the graduates of this program have stayed to become faculty in our Department. As Chief of Physics, I am responsible for the physics education of the medical residents. I have also taken responsibility for mentoring new faculty in the Physics Division as well as clinical physics instruction for new medical faculty. In summary, it is my responsibility to educate all faculty and staff in the physics of Radiation Oncology.

RESEARCH AND CREATIVE ACTIVITIES**RESEARCH AWARDS AND GRANTS**CURRENT

U56 Minority Institution/Cancer Center Partnership	04/01/02-03/31/07
Cancer Training and Career Development	\$2,500,000 direct
NIH/NCI (PI: Macher)	

Siemens – UCSF Research Collaborative Agreement	10/01/05-09/30/07
Research on Portal Imaging and Intensity Modulation	\$390,000 direct
Siemens Oncology Systems (PI: Verhey)	

PENDING

Radiosurgical Treatment of Temporal Lobe Epilepsy
NIH/NINDS (PI: Barbaro)

PAST

R01 NS39280	09/30/00-08/31/03
Radiosurgical Treatment of Temporal Lobe Epilepsy	\$266,481 direct
NIH/NINDS (PI: Barbaro)	

Award for Physics Residency Training Program	09/01/96-08/31/98
ASTRO/AAPM (PI: Verhey)	\$30,000 direct

PEER REVIEWED PUBLICATIONS

1. Abrams RJ, Abashian A, Mischke RE, Nefkens BMK, Smith JH, Thatcher RC, Verhey LJ, Wattenberg A. Test of time reversal invariance in the decay $K_L^0 \rightarrow \pi^- \mu^+ \nu$. Phys Rev Letters 17:606-608, 1966.
2. Verhey LJ, Nefkens BMK, Abashian A, Abrams RJ, Carpenter DW, Mischke RE, Smith JH, Thatcher RC, Wattenberg A. Experimental investigation of CP violation in $K_e 3^0$ decays. Phys Rev Letters 17:669-671, 1966.
3. Mischke RE, Abashian A, Abrams RJ, Carpenter DW, Nefkens BMK, Smith JH, Thatcher RC, Verhey LJ, Wattenberg A. Determination of the phase of the CP-nonconservation parameter η_{\pm} in neutral K decay. Phys Rev Letters 18:138-141, 1967.
4. Thatcher RC, Abashian A, Abrams RJ, Carpenter DW, Mischke RE, Nefkens BMK, Smith JH, Verhey LJ, Wattenberg A. Upper limit on the decay rate $K_L^0 \rightarrow \pi^+ \pi^- \gamma$ Phys Rev. D4:1674-1680, 1968.
5. Abrams RJ, Abashian A, Mischke RE, Nefkens BMK, Smith JH, Thatcher RC, Verhey LJ, Wattenberg A. Muon polarization in $K \mu 3^0$ meson decay. Phys Rev. D5:1603-1615, 1968.
6. Parsons ASL, Truol P, Berardo PA, Haddock RP, Verhey LJ, Zeller ME. A scintillation counter array for detection of high energy neutrons. Nuc Inst and Methods 79:43-50, 1970.
7. Berardo PA, Haddock RP, Nefkens BMK, Verhey LJ, Zeller ME, Parsons ASL, Truol P. Measurement of the $\pi^- p \rightarrow \gamma n$ differential cross section near the ρ resonance, P_{11} (1460). Phys Rev Letters 24:419-422, 1970.
8. Berardo PA, Haddock RP, Nefkens BMK, Verhey LJ, Zeller ME, Parsons ASL, Truol P. Measurement of inverse pion photoproduction near the P_{33}^0 (1236) resonance. Phys Rev Letters 26:201-204, 1971.
9. Berardo PA, Haddock RP, Helland J, Nefkens BMK, Verhey LJ, Zeller ME, Parsons ASL, Truol P. Analysis of negative pion photoproduction near the P_{33} resonance: test of the $\Delta I \leq 1$ rule and T-reversal invariance. Phys Rev Letters 26:205-208, 1971.
10. Berardo PA, Haddock RP, Nefkens BMK, Verhey LJ, Zeller ME, Parsons ASL, Truol P. A measurement of the differential cross-section $\pi^- p \rightarrow n \pi^0$. Phys Rev D6:756-766, 1972.
11. Berardo PA, Haddock RP, Nefkens BMK, Verhey LJ, Zeller ME, Parsons ASL, Truol P. Differential cross-sections of $\pi^- p \rightarrow \gamma n$ for 317, 452 and 491 MeV/c incident pion momentum. Phys Rev. D9:621-643, 1974.
12. Comiso JC, Blasberg DJ, Haddock RP, Nefkens BMK, Truol P, Verhey LJ. Inverse pion photoproduction in the vicinity of the P_{33} (1232) resonance and a test of time reversal invariance. Phys Rev. D12:719-737, 1975.
13. Comiso JC, Blasberg DJ, Haddock RP, Nefkens BMK, Truol P, Verhey LJ. Differential cross-section measurements of $\pi^- p \rightarrow \pi^0 n$ around the P_{33} (1232) resonance. Phys. Rev. D12:738-743, 1975.
14. Loomis WA, Matis HS, Anderson HL, Bharadwaj VK, Booth NE, Fine RM, Francis WR, Gordon BA, Heisterberg RH, Hicks RG, Kirk TBW, Kirkbride GI, Mo LW, Myrianthopoulos LC, Pipkin RM, Pordes SH, Quirk SC. Inclusive hadron production in inelastic muon-proton scattering at 150 GeV/c. Phys Rev Letters 35:1483, 1975.

15. Weiss AJ, Blasberg DJ, Comiso JC, Haddock RP, Nefkens BMK, Verhey LJ, Zeller MB, Crowe KM, Fainberg A, Truol P. Measurement of differential cross-sections for radiative pion-proton capture in the second resonance region. *Nuc Phys. B* 101:1-18, 1975.
16. Anderson HL, Bharadwaj VK, Booth NE, Fine RM, Francis WR, Gordon BA, Heisterberg RH, Hicks RG, Kirk TBW, Kirkbride GI, Loomis WA, Matis HS, Mo LW, Myrianthopoulos LC, Pipkin FM, Pordes SH, Quirk SW, Shambroom WD, Skuja A, Verhey LJ, Williams WSC, Wilson R, Wright SC. Properties of inclusive hadron spectra in muon-nucleon scattering at 150 GeV/c. *Phys Rev Letters* 36:1422-1425, 1976.
17. Anderson HL, Bharadwaj VK, Booth NE, Fine RM, Francis WR, Gordon BA, Heisterberg RH, Hicks RG, Kirk TBW, Kirkbride GI, Loomis WA, Matis HS, Mo LW, Myrianthopoulos LC, Pipkin FM, Pordes SH, Quirk TW, Shambroom WD, Skuja A, Verhey LJ, Williams WSC, Wilson R, Wright SC. Measurement of nucleon structure function in muon scattering at 147 GeV/c. *Phys Rev Letters* 37:4-7, 1976.
18. Gragoudas ES, Goitein M, Koehler AM, Verhey LJ, Tepper J, Suit HD, Brockhurst R, Constable IJ. Proton irradiation of small choroidal malignant melanomas. *Am J Ophthalmol.* 83:665-673, 1977.
19. Francis WR, Anderson HL, Bharadwaj VK, Booth NE, Fine RM, Gordon BA, Heisterberg RH, Hicks RG, Kirk TBW, Kirkbride GI, Loomis WA, Matis HS, Mo LW, Myrianthopoulos LC, Pipkin FM, Pordes SH, Quirk TW, Shambroom WD, Skuja A, Verhey LJ, Williams WSC, Wilson R, Wright SC. Diffractive production of mesons by 147-GeV muons. *Phys Rev Letters* 38:633-636, 1977.
20. Anderson HL, Bharadwaj VK, Booth NE, Fine RM, Francis WR, Gordon BA, Heisterberg RH, Hicks RG, Kirk TBW, Kirkbride GI, Loomis WA, Matis HS, Mo LW, Myrianthopoulos LC, Pipkin FM, Pordes SH, Quirk TW, Shambroom WD, Skuja A, Staton MA, Williams WSC, Verhey LJ, Wilson R, Wright SC. Measurement of the proton structure function from muon scattering. *Phys Rev Letters* 38:1450-1454, 1977.
21. Tepper J, Verhey L, Goitein M, Suit HD, Koehler AM. In vivo determinations of RBE in a high energy modulated proton beam using normal tissue reactions and fractionated dose schedules. *Int J Radiat Oncol Biol Phys.* 2:1115-1122, 1977.
22. Suit H, Goitein M, Tepper J, Verhey L, Koehler A, Schneider R, Gragoudas E. Clinical experience and expectation with protons and heavy ions. *Int J Radiat Oncol Biol Phys.* 3:115-125, 1977.
23. Gragoudas E, Goitein M, Koehler A, Wagner M, Verhey L, Tepper J, Suit H, Schneider R, Johnson K. Proton irradiation of choroidal melanomas. *Arch Ophthalmol.* 96:1583-1591, 1978.
24. Gragoudas E, Goitein M, Koehler A, Wagner M, Verhey L, Tepper J, Suit H, Schneider R, Johnson K. Proton irradiation of malignant melanoma of the ciliary body. *Brit J Ophthalmol.* 63:135-139, 1979.
25. Shipley W, Tepper J, Prout G, Verhey L, Mendingo O, Goitein M, Koehler A, Suit H. Proton radiation as boost therapy for localized prostatic carcinoma. *JAMA* 241:1912-1915, 1979.
26. Verhey L, Koehler A, McDonald J, Goitein M, Ma I-C, Schneider R, Wagner M. The determination of absorbed dose in a proton beam for purposes of charged particle radiation therapy. *Radiat Res.* 79:34-54, 1979.
27. Suit HD, Goitein M, Munzenrider JE, Verhey L, Gragoudas E, Koehler AM, Urano M, Shipley WU, Linggood RM, Friedberg C, Wagner M. Clinical experience with proton beam radiation therapy. *J Canad Assoc Radiol.* 31:35-39, 1980.

28. Gragoudas E, Goitein M, Verhey L, Munzenrider J, Suit H, Koehler A. Proton beam irradiation: an alternative to enucleation for intra-ocular melanomas. *Ophthalmol.* 87:571-581, 1980.
29. Urano M, Goitein M, Verhey L, Mendiondo O, Suit H, Koehler A. Relative Biological effectiveness of a high energy modulated proton beam using a spontaneous murine tumor in vivo. *Int J Radiat Oncol Biol Phys.* 6:1187-1193, 1980.
30. Munzenrider JE, Shipley WU, Verhey LJ. Future prospects of radiation therapy with protons. *Sem Oncol.* 8:110-124, 1981.
31. Shambroom WD, Gordon BA, Loomis WA, Pipkin FM, Pordes SH, Verhey LJ, Wilson R, Anderson HL, Fine RM, Heisterberg RH, Matis HS, Mo LW, Myrianthopoulos LC, Wright SC, Francis WR, Hicks WR, Kirk TBW, Bharadwaj VK, Booth NE, Kirkbride GI, Quirk TW, Skuja A, Williams WSC. Coherent production of mesons in muon-carbon scattering at 150 and 100 GeV. *Phys Rev.* 24:775-777, 1981.
32. Verhey LJ, Goitein M, McNulty P, Munzenrider JE, Suit HD. Precise positioning of patients for radiation therapy. *Int J Radiat Oncol Biol Phys.* 8:289-294, 1982.
33. Suit HD, Goitein M, Munzenrider J, Verhey L, Davis KR, Koehler A, Linggood R, Ojemann RG. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. *J Neurosurg.* 56:377-385, 1982.
34. Gragoudas ES, Goitein M, Verhey L, Munzenrider J, Urie M, Suit H, Koehler A. Proton beam irradiation of uveal melanomas: results of 5 ½ year study. *Arch Ophthalmol.* 100:928-934, 1982.
35. Goitein M, Abrams M, Gentry R, Urie M, Verhey L, Wagner M. Planning treatment with heavy charged particles. *Int J Radiat Oncol Biol Phys.* 8:2065-2070, 1982.
36. Suit HD, Goitein M, Munzenrider J, Verhey L, Blitzer P, Gragoudas E, Koehler AM, Urie M, Gentry R, Shipley W, Urano M, Duttenhaver J, Wagner M. Evaluation of the clinical applicability of proton beams in definitive fractionated radiation therapy. *Int J Radiat Oncol Biol Phys.* 8:2199-2205, 1982.
37. Duttenhaver JR, Shipley WU, Perrone T, Verhey LJ, Goitein M, Munzenrider JE, Prout GR, Kerr WS, Parkhurst EC, Suit HD. Protons or megavoltage x-rays as boost therapy for patients irradiated for localized prostatic carcinoma: an early phase I/II comparison. *Cancer* 51:1599-1604, 1983.
38. Verhey LJ, Sedlacek R. Determination of the radioprotective effects of topical applications of MEA, WR-2721 and N-acetylcysteine on murine skin. *Radiat Res.* 93:175-183, 1983.
39. Urano M, Verhey LJ, Goitein M, Tepper JE, Suit HD, Mendiondo O, Gragoudas ES, Koehler A. Relative biological effectiveness of modulated proton beams in various murine tissues. *Int J Radiat Oncol Biol Phys.* 10:509-514, 1984.
40. Gragoudas ES, Goitein M, Seddon J, Verhey L, Munzenrider J, Urie M, Suit HD, Blitzer P, Johnson KN, Koehler A. Preliminary results of proton beam irradiation of macular and paramacular melanomas. *Brit J Ophthalmol.* 68:479-485, 1984.
41. Gragoudas ES, Seddon J, Goitein M, Verhey L, Munzenrider J, Urie M, Suit HD, Blitzer P, Koehler A. Current results of proton beam irradiation of uveal melanomas. *Ophthalmology* 92:284-291, 1985.
42. Austin-Seymour M, Munzenrider JE, Goitein M, Gentry R, Gragoudas E, Koehler AM, McNulty P, Osborne E, Ryugo DK, Seddon J, Urie M, Verhey L, Suit HD. Progress in low LET heavy particle therapy: intracranial and paracranial tumors and uveal melanomas. *Radiat Res.* 104:S219-S226, 1985.

43. Seddon JM, Gragoudas ES, Polivogianis L, Hsieh CC, Egan KM, Goitein M, Verhey L, Munzenrider J, Austin-Seymour M, Urie M, Koehler A. Visual outcome after proton beam irradiation of uveal melanoma. *Ophthalmol.* 93:666-674, 1986.
44. Gragoudas ES, Seddon JM, Egan KM, Polivogianis L, Hsieh CC, Goitein M, Verhey L, Munzenrider J, Austin-Seymour M, Urie M, Koehler A. Prognostic factors for metastasis following proton beam irradiation of uveal melanomas. *Ophthalmol.* 93:675-680, 1986.
45. Petti PL, Verhey L, Wilson R. A measurement of w for 150 MeV protons in nitrogen and argon. *Phys. Med. Biol.* 31:1129-1138, 1986.
46. Gragoudas ES, Seddon JM, Egan K, Glynn R, Munzenrider J, Austin-Seymour M, Goitein M, Verhey L, Urie M, Koehler A. Long-term Results of Proton Beam Irradiated Uveal Melanomas. *Ophthalmol.* 94:349-353, 1987.
47. Seddon JS, Gragoudas ES, Egan KM, Glynn RJ, Munzenrider JE, Austin-Seymour M, Goitein M, Verhey L, Urie M, Koehler A. Uveal Melanomas Near the Optic Disc or Fovea: Visual Results after Proton Beam Irradiation. *Ophthalmol.* 94: 354-361, 1987.
48. Suit HD, Phil D, Becht J, Leong J, Stracher M, Wood WC, Verhey L, Goitein M. Potential for Improvement in Radiation Therapy. *Int. J. Radiation Oncology Biol. Phys.* 14:777-786, 1988.
49. Gragoudas ES, Seddon JM, Egan KM, Glynn RJ, Goitein M, Munzenrider J, Verhey L, Urie M, Koehler A. Metastasis from Uveal Melanoma after Proton Beam Irradiation. *Ophthalmol.* 95: 992-999, 1988.
50. Suit HD, Griffin TW, Castro JR, Verhey LJ. Particle Radiation Therapy Research Plan. *Amer. J. Clin. Oncol.* 11:330-341, 1988.
51. Suit HD, Verhey L. Precision in Radiotherapy: Precision in megavoltage radiotherapy. *British J Radiol.* 22:17-24, 1988.
52. Munzenrider JE, Gragoudas E, Seddon J, Sisterson J, McNulty P, Birnbaum S, Johnson K, Austin-Seymour M, Slater J, Goitein M, Verhey L, Urie M, Ruotolo D, Egan K, Osuna F. Conservative treatment of uveal melanoma: probability of eye retention after proton treatment. *Int. J. Radiat. Oncol. Biol. Phys.* 15:553-558, 1988.
53. Slater JD, Austin-Seymour M, Munzenrider J, Birnbaum S, Carroll R, Klibanski A, Riskind P, Urie M, Verhey L, Goitein M. Endocrine Function Following High Dose Proton Therapy for Tumor of the Upper Clivus, *Int. J. Radiat. Oncol. Biol. Phys.* 15:607-611, 1988.
54. Suit HD, Sedlacek R, Silver G, Hsieh CC, Epp ER, Ngo FQ, Roberts WK, Verhey L. Therapeutic Gain Factors for Fractionated Radiation Treatment of Spontaneous Murine Tumors Using Fast Neutrons, Photons Plus 0₂1 or 3 ATA, or Photons Plus Misonidazole. *Radiat. Research* 116:482-502, 1988.
55. Austin-Seymour M, Munzenrider J, Goitein M, Verhey L, Urie M, Gentry R, Birnbaum S, Ruotolo D, McManus P, Skates S, Ojemann R, Rosenberg A, Schiller A, Koehler A, Suit H. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 70:13-17, 1989.
56. Rabin MSZ, Gottschalk B., Koehler A., Sisterson J., Verhey LJ. Compact designs for comprehensive proton beam clinical facilities. *Nuclear Instruments and Methods in Physics Research B40/41: 1335-1339*, 1989.
57. Habrand JL, Austin-Seymour M, Birnbaum S, Wray S, Carroll R, Munzenrider JE, Verhey LJ, Urie M, Goitein M. Neurovisual Outcome Following Proton Radiation Therapy. *Int. J. of Radiat Oncol Biol Phys.* 16: 1601-1606, 1989.

58. Munzenrider JE, Verhey LJ, Gragoudas ES, Seddon JM, Urie M, Gentry R, Birnbaum S, Ruotolo DM, Crowell C, McManus P, Finn S, Sisterson J, Johnson K, Egan K, Lento D., Bassin P. Conservative Treatment of Uveal Melanoma: Local Recurrence after Proton Beam Therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 17: 493-498, 1989.
59. Egan KM, Gragoudas ES, Seddon JM, Glynn RJ, Munzenrider JE, Goitein M, Verhey L, Urie M, Koehler A. The Risk of Enucleation after Proton Beam Irradiation of Uveal Melanoma. *Ophthalmol.* 96: 1377-1383, 1989.
60. Dicello JF, Lyman JT, McDonald JC, Verhey LJ. A portable system for microdosimetric intercomparison by Task Group #20 of the American Association of Physicists in medicine (AAPM). *Nuclear Instruments and Methods in Physics Research B45*: 724-729, 1990.
61. Austin-Seymour M, Urie M, Munzenrider JE, Goitein M, Verhey LJ, Gentry R, McNulty P, Koehler A, Suit HD. Considerations in Fractionated Proton Radiation Therapy: Clinical potential and results. *Radiotherapy and Oncology* 17: 29-35, 1990.
62. Suit HD, Goitein M, Munzenrider JE, Verhey LJ, Urie M, Gragoudas ES, Koehler A, Gottschalk B, Sisterson J, Tatsuzaki H, Miralbell R. Increased Efficacy of Radiation Therapy by use of Proton Beam. *Strahlenther. Oncol.* 166: 40-44 (Nr. 1), 1990.
63. Austin-Seymour M, Munzenrider J, Linggood R, Goitein M, Verhey L, Urie M, Gentry R, Birnbaum S, Ruotolo D, Crowell C, McManus P, Skates S, Koehler A, Suit H. Fractionated Proton Radiation Therapy of Cranial and Intracranial Tumors. *Am J of Clinical Oncol.* 13(4): 327-330, 1990.
64. Hiraoka T, Kawashima K, Hoshino K, Kawachi K, Kanai T, Ito A, Verhey L, McDonald JC, Ma I-C. Small Scale Proton Dosimetry Intercomparison between Japan and USA. *Jpn. Radiol. Phys.* 9(3): 135-141, 1989.
65. Dugan T, Shipley W, Young R, Verhey L, Althausen A, Heney N, McManus P, Abraham A. Biopsy after External Beam Radiation Therapy for Adenocarcinoma of the Prostate: Correlation with Original Histologic Grade and Current Prostatic Antigen Levels. *Journal of Urology* 146: 1313-1316, 1991.
66. Verhey L and Lyman J. Some Considerations Regarding w Values for Heavy Charged-Particle Radiotherapy. *Medical Physics* 19(1): 151-153, 1992.
67. Schulz RJ, Verhey LJ, Huq MS, Venkataramanan N. Water-Calorimeter Dosimetry for 160 MeV Protons. *Phys. Med. Biol.* 37(4): 947-3, 1992.
68. Gall KP, Verhey L, Alonso J, Castro J, Collier JM, Chu W, Daftari I, Goitein M, Kubo H, Ludewigt B, Munzenrider J, Petti P, Renner T, Rosenthal S, Smith A, Staples J, Suit H, Thornton A. State of the Art? New proton medical facilities for the Massachusetts General Hospital and the University of California Davis Medical Center. *Nuc. Inst. Methods B79*: 881-884, 1993.
69. Gall KP, Verhey LJ, Wagner M. Computer-Assisted Positioning of Radiotherapy Patients using Implanted Radiopaque Fiducials. *Med. Phys.* 20(4): 1153-1159, 1993.
70. Roach M, Pickett B, Rosenthal SA, Verhey L, Phillips TL. Defining Treatment Margins for Six Field Conformal Irradiation of Localized Prostate Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 28: 267-275, 1993.
71. Zhou S, Verhey LJ. A robust method of multileaf (MLC) leaf-configuration verification. *Phys. Med. Biol.* 39: 1929-1947, 1994.
72. Pickett B, Roach M, Horine P, Verhey L, Phillips TL. Optimization of the oblique angles in the treatment of prostate cancer during six-field conformal radiotherapy. *Medical Dosimetry* 19: 237-254, 1994.

73. Yu CX, Yan D, Du MN, Zhou S, Verhey LJ. Optimization of leaf positions when shaping a radiation field with a multileaf collimator. *Phys. Med. Biol.* 40: 305-308, 1995.
74. Wara W, Bauman G, Gutin P, Ciricillo S, Larson D, McDermott M, Sneed P, Verhey L, Smith V, Petti P, Edwards M: Stereotactic Radiosurgery in Children. *Stereotact. Func. Neurosurg.* 64(syoo, 1): 118-125, 1995.
75. Shipley WU, Verhey LJ, Munzenrider JE, Suit HD, Urie MM, McManus PL, Young RH, Shipley JW, Zietman AL, Biggs PJ, Heney NM, Goitein M. Advanced Prostate Cancer: The Results of a Randomized Comparative Trial of High Dose Irradiation Boosting with Conformal Protons Compared with Conventional Dose Irradiation Using Photons Alone. *Int. J. Radiat. Oncol. Biol. Phys.* 32: 3-12, 1995.
76. Pickett B, Roach M, Verhey L, Horine P, Malfatti C, Akazawa C, Dea D, Varad B, Rathbun C, Phillips TL. The Value of Nonuniform Margins for Six-Field Conformal Irradiation of Localized Prostate Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 32: 211-218, 1995.
77. Serago CF, Thornton AF, Urie MM, Chapman P, Verhey L, Rosenthal SJ, Gall KP, Niemierko A. Comparison of proton and x-ray conformal dose distributions for radiosurgery applications. *Med. Phys.* 22(12): 2111-2116, 1995.
78. McDermott MW, Sneed PK, Chang SM, Gutin PH, Wara WM, Verhey LJ, Smith V, Petti PL, Ho M, Park E, Edwards MSB, Prados MD, Larson DA. Results of Radiosurgery for Recurrent Gliomas. in Kondziolka D (ed): *Radiosurgery 1995*. Basel, Karger, 1996, vol 1, pp 102-112.
79. Baumann GS, Wara WM, Larson DA, Sneed PK, Gutin PH, Ciricillo SF, McDermott MW, Park E, Stalpers LJ, Verhey LJ, et al. Gamma Knife radiosurgery in children. *Pediatric Neurosurgery* 24(4): 193-201, 1996.
80. Verhey LJ. 3-D Conformal Therapy using Beam Intensity Modulation. in Meyer JL, Purdy JA (eds): *3-D Conformal Radiotherapy*. Front. Radiat. Ther. Oncol. Basel, Karger, 1996, vol 29, pp 139-155.
81. Roach III M, Pickett B, Weil M, Verhey L. The "Critical Volume Tolerance Method" for estimating the limits of dose escalation during three-dimensional conformal radiotherapy for prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 35(5): 1019-1025, 1996.
82. Daftari IK, Renner TR, Verhey LJ, Singh RP, Nyman M, Petti PL, Castro JR. New UCSF proton ocular beam facility at the Crocker Nuclear Laboratory Cyclotron (UC Davis). *Nuc. Inst. and Methods in Phys. Res.* A380: 597-612, 1996.
83. Shu H-K, Sneed PK, Shiau C-Y, McDermott MW, Lamborn KR, Park E, Ho M, Petti PL, Smith V, Verhey LJ, Wara WM, Gutin PH, Larson DA. Factors influencing survival after Gamma Knife radiosurgery for patients with single and multiple brain metastases. *The Cancer Journal from Scientific American* 2(6): 335-342, 1996.
84. Vatnitsky S, Siebers J, Miller D, Moyers M, Schaefer M, Jones D, Vynckier S, Hayakawa Y, Delacroix S, Isacson U, Medin J, Kacperek A, Lomax A, Coray A, Kluge H, Heese J, Verhey L, Daftari I, Gall K, Lam G, Beck T, Hartmann G. Proton dosimetry intercomparison. *Radiosurgery and Oncology* 41: 169-177, 1996.
85. Shiau C-Y, Sneed PK, Shu H-K, Lamborn KR, McDermott MW, Chang S, Nowak P, Petti PL, Smith V, Verhey LJ, Ho M, Park E, Wara WM, Gutin PH, Larson DA. Radiosurgery for brain metastasis: Relationship of dose and pattern of enhancement to local control. *Int. J. Radiat. Oncol. Biol. Phys.* 37(2): 375-383, 1997.
86. Daftari IK, Char DH, Verhey LJ, Castro JR, Petti PL, Meecham WJ, Kroll S, Blakely EA. Anterior segment sparing to reduce charged particle radiotherapy complications in uveal melanoma. *Int. J. Radiat. Oncol. Biol. Phys.* 39(5):997-1010, 1997.

87. Nelson SJ, Huhn S, Vigneron DB, Day MR, Wald LL, Prados M, Chang S, Gutin PH, Sneed PK, Verhey L, Hawkins RA, Dillon WP. Volume MRI and MRSI techniques for the quantitation of treatment response in brain tumors: Presentation of a detailed case study. *JMRI* 7(6): 1146-1152, 1997.
88. Verhey LJ, Smith V, Serago CS. Comparison of radiosurgery treatment modalities based on physical dose distributions. *Int. J. Radiat. Oncol. Biol. Phys.* 40(2): 497-505, 1998.
89. Smith V, Verhey LJ, Serago CS. Comparison of radiosurgery treatment modalities based on complication and control probabilities. *Int. J. Radiat. Oncol. Biol. Phys.* 40(2): 507-513, 1998.
90. Seung SK, Sneed PK, McDermott MW, Shu HK, Leong SP, Chang S, Petti PL, Smith V, Verhey LJ, Wara WM, Gutin PH, Phillips TL, Larson DA. Gamma Knife radiosurgery for malignant brain metastases. *Cancer Journal from Scientific American* 4(2): 103-109, 1998.
91. Xia P, Verhey LJ. MLC leaf sequencing algorithm for intensity modulated beams with multiple static segments. *Medical Physics* 25(8): 1424-1434, 1998.
92. Verhey, LJ. Comparison of Three-dimensional Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy Systems. *Sem. in Rad. Onc.* 9(1): 78-98, 1999.
93. Vatnitsky S, Moyers M, Miller D, Abell G, Slater JM, Pedroni E, Coray A, Mazal, A, Newhauser W, Jaekel O, Heese J, Fukumura A, Futami Y, Verhey L, Daftari I, Grusell E, Molokanov A, Block C. Proton dosimetry intercomparison based on the ICRU 59 protocol. *Radiotherapy and Oncology* 51: 273-279, 1999.
94. Pickett B, Vigneault E, Kurhanewicz J, Verhey L, Roach M. Static field intensity modulation to treat a dominant intra-prostatic lesion to 90 Gy compared to seven field 3-dimensional radiotherapy. *Int. J. Radiation Oncology Biol. Phys.* 43(4): 921-929, 1999.
95. Daftari I, Castenadas C, Petti PL, Singh RP, Verhey LJ. An application of GafChromic MD-55 film for 67.5 MeV clinical proton beam dosimetry. *Phys. Med. Biol.* 44: 2735-2745, 1999.
96. Ma L, Xia P, Verhey LJ, Boyer AL. A dosimetric comparison of fan-beam intensity modulated radiotherapy with gamma knife stereotactic radiosurgery for treating intermediate intracranial lesions. *Int. J. Radiation Oncology Biol. Phys.* 45(5): 1325-1330, 1999.
97. Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Int. J. Radiation Oncology Biol. Phys.* 48(2):329-337, 2000.
98. Graves EE, Nelson SJ, Vigneron DB, Chin C, Verhey L, McDermott M, Larson D, Sneed PK, Chang S, Prados MD, Lamborn K, Dillon WP. A preliminary study of the prognostic value of proton magnetic resonance spectroscopic imaging in Gamma Knife radiosurgery of recurrent malignant gliomas. *Neurosurgery* 46(2): 319-328, 2000.
99. Verhey LJ. Physical Considerations in the Use of Intensity Modulated Radiotherapy to Produce Three-Dimensional Conformal Dose Distributions. *J. Jpn. Soc. Ther. Radiol. Oncol.* 12: 191-203, 2000.
100. Sultanem K, Shu H-K, Xia P, Akazawa C, Quivey JM, Verhey LJ, Fu KK. Three-dimensional intensity-modulated radiotherapy in treatment of nasopharyngeal carcinoma: The University of California-San Francisco experience. *Int J. Radiation Oncology Biol. Phys.* 48(3): 711-722, 2000.
101. Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Int. J. Radiation Oncology Biol. Phys.* 48(2):329-337, 2000.
102. Posner MD, Quivey JM, Akazawa PF, Xia P, Akazawa C, Verhey LJ. Dose optimization for the treatment of anaplastic thyroid carcinoma: A comparison of treatment planning techniques. *Int J. Radiation Oncology Biol Phys.* 48(2):475-483, 2000.

103. Ojemann SG, Sneed PK, Larson DA, Gutin PH, Berger MS, Verhey L, Smith V, Petti P, Wara W, Park E, McDermott MW. Radiosurgery for malignant meningioma: results in 22 patients. *J. Neurosurg.* (Suppl 3) 93:62-67, 2000.
104. Pirzkall A, McKnight TR, Graves EE, Carol MP, Sneed PK, Wara WW, Nelson SJ, Verhey LJ, Larson DA. MR-spectroscopy guided target delineation for high-grade gliomas. *Int J Radiat Oncol Biol Phys.* 50(4):915-28, 2001.
105. Hartmann Siantar CL, Walling RS, Daly TP, Faddegon B, Albright N, Bergstrom P, Bielajew AF, Chuang C, Garrett D, House RK, Knapp D, Wieczorek DJ, Verhey LJ. Description and dosimetric verification of the PEREGRINE Monte Carlo dose calculation system for photon beams incident on a water phantom. *Med. Phys.* 28(7): 1322-1337, 2001.
106. Xia P, Verhey LJ: Delivery Systems of Intensity-Modulated Radiotherapy Using Conventional Multileaf Collimators. *Medical Dosimetry* 26(2): 169-177, 2001.
107. Xia P, Pickett B, Vigneault E, Verhey LJ, Roach III M. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 Gy. *Int. J. Radiation Oncology Biol. Phys.* 51(1): 244-254, 2001.
108. Graves EE, Pirzkall A, Nelson SJ, Verhey LJ, Larson DA: Registration of magnetic resonance spectroscopic imaging to computed tomography for radiotherapy treatment planning. *Med. Phys.* 28(12): 2489-2496, 2001.
109. Michalski J, Purdy JA, Gaspar L, Souhami L, Ballow M, Bradley J, Chao CK, Crane C, Eisbruch A, Followill D, Forster K, Fowler J, Gillin MT, Graham ML, Harms WB, Huq MS, Kline RW, Mackie TR, Mukherji S, Podgorsak EB, Roach M, Ryu, J, Sandler H, Schultz CJ, Schell M, Verhey LJ, Vicini F, Winter KA: Radiation Therapy Oncology Group Research Plan 2002-2006. Image Guided Radiation Therapy Committee. *Int J Radiat Oncol Biol Phys.* 51(3 Suppl2):60-65, 2001.
110. Intensity Modulated Radiation Therapy Collaborative Working Group: Boyer AL, Butler EB, DiPetrillo TA, Engler MJ, Fraass B, Grant III W, Ling CC, Low DA, Mackie TR, Mohan R, Purdy JA, Roach M, Rosenman JG, Verhey LJ, Wong JW: Intensity-modulated radiotherapy: Current status and issues of interest. *Int. J. Radiation Oncology Biol. Phys.* 51(4): 880-914, 2001.
111. Nakamura JL, Verhey LJ, Smith V, Petti PL, Lamborn KR, Larson DA, Wara WM, McDermott MW, Sneed PK: Dose conformity of gamma knife radiosurgery and risk factors for complications. *Int. J. Radiation Oncology Biol. Phys.* 51(5): 1313-1319, 2001. Xia P, Chuang CF, Verhey LJ: Communication and sampling rate limitations in IMRT delivery with a dynamic multileaf collimator system. *Med. Phys.* 29(3): 412-423, 2002.
112. Xia P, Chuang CF, Verhey LJ: Communication and sampling rate limitations in IMRT delivery with a dynamic multileaf collimator system. *Med. Phys.* 29(3): 412-423, 2002.
113. Pirzkall A, Carol MP, Pickett B, Xia P, Roach III M, Verhey LJ: The effect of beam energy and number of fields on photon-based IMRT for deep-seated targets. *Int J Radiat Oncol Biol Phys.* 53(2): 434-442, 2002.
114. Lee N, Chuang C, Quivey JM, Phillips TL, Akazawa P, Verhey LJ, Xia P: Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *Int. J. Radiation Oncology Biol. Phys.* 53(3): 630-637, 2002.
115. Xia P, Hwang AB, Verhey LJ: A leaf sequencing algorithm to enlarge treatment field length in IMRT. *Med. Phys.* 29(6): 991-998, 2002.
116. Chuang CF, Verhey LJ, Xia P: Investigation of the use of MOSFET for clinical IMRT dosimetric verification. *Med. Phys.* 29(6): 1109-1115, 2002.

117. Verhey LJ: Issues in optimization for planning of intensity-modulated radiation therapy. *Seminars in Radiation Oncology* 12(3): 210-218, 2002.
118. Pirzkall A, Nelson SJ, McKnight TR, Takahashi MM, Li X, Graves EE, Verhey LJ, Wara WM, Larson DA, Sneed PK: Metabolic imaging of low-grade gliomas with three-dimensional magnetic resonance spectroscopy. *Int J Radiat Oncol Phys.* 53(5): 1254-1264, 2002.
119. Cardenas LR, Cheng KH, Verhey LJ, Xia P, Davis L, Cannon B: A self consistent normalized calibration protocol for three dimensional magnetic resonance gel dosimetry. *Magnetic Resonance Imaging* 20: 667-679, 2002.
120. Nakamura JL, Pirzkall A, Carol MP, Xia P, Smith V, Wara WM, Petti PL, Verhey LJ, Sneed PK: Comparison of intensity-modulated radiosurgery with Gamma Knife radiosurgery for challenging skull base lesions. *Int. J. Radiation Oncol Biol Phys.* 55(1): 99-109, 2003.
121. Huang D, Xia P, Akazawa P, Akazawa C, Quivey JM, Verhey LJ, Kaplan M: Comparison of treatment plans using intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys.* 56(1):158-68, 2003.
122. Langen KM, Pouliot J, Anezinos C, Aubin M, Gottschalk AR, Hsu I-C, Lowther D, Liu Y-M, Shinohara K, Verhey LJ, Weinberg V, Roach III M: Evaluation of ultrasound-based prostate localization for image-guided radiotherapy. *Int J Radiat Oncol Biol Phys.* 57(3): 635-644, 2003.
123. Pirzkall A, Li X, Oh J, Chang S, Berger MS, Larson DA, Verhey LJ, Dillon WP, Nelson SJ: 3D MRSI for resected high-grade gliomas before RT: tumor extent according to metabolic activity in relation to MRI. *Int J Radiat Oncol Biol Phys.* 59(1): 126-137, 2004
124. Lee N, Akazawa C, Akazawa P, Quivey JM, Tang C, Verhey LJ, Xia P: A forward-planned treatment technique using multisegments in the treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 59(2): 584-594, 2004.
125. Xia P, Lee N, Liu YM, Poon I, Weinberg V, Shin E, Quivey JM, Verhey LJ: A study of planning dose constraints for treatment of nasopharyngeal carcinoma using a commercial inverse treatment planning system. *Int J Radiat Oncol Biol Phys* 59(3): 886-896, 2004.
126. Chan AA, Lau A, Pirzkall A, Chang SM, Verhey LJ, Larson D, McDermott MW, Dillon WP, Nelson SJ: Proton magnetic resonance spectroscopic imaging as a tool for evaluating Grade IV glioma patients undergoing gamma knife radiosurgery. *J Neurosurg* 101(3): 467-475, 2004.
127. Pouliot J, Bani-Hashemi A, Chen J, Svatos M, Ghelmansarai F, Mitschke M, Aubin M, Xia P, Morin O, Bucci K, Roach III M, Hernandez P, Zheng Z, Hristov D, Verhey L: Low-dose megavoltage cone-beam CT for radiation therapy. *Int. J. Radiation Oncology Biol. Phys.* 61(2): 552-560, 2005.
128. Xia P, Yu N, Xing L, Sun X, Verhey LJ: Investigation of using a power function as a cost function in inverse planning optimization. *Med Phys.* 32(4): 920-927, 2005.
129. Park CS, Kim Y, Lee N, Bucci KM, Quivey JM, Verhey LJ, Xia P: Method to account for dose fractionation in analysis of IMRT plans: modified equivalent dose. *Int J Radiat Oncol Biol Phys* 62(3): 925-932, 2005.
130. Verhey LJ, Chen CC, Chapman P, Loeffler J, Curry WT: Single-fraction stereotactic radiosurgery for intracranial targets. *Neurosurg Clin N Am.* 17(2): 79-97, 2006.
131. Kim Y, Verhey LJ, Xia P: A feasibility study of using conventional jaws to deliver IMRT plans in the treatment of prostate cancer. *Phys Med Biol.* 52(8): 2147-56, 2007

NON-PEER REVIEWED PUBLICATIONS AND OTHER CREATIVE ACTIVITIES

Significant Reports

1. W. T. Chu, J. W. Staples, B. A. Ludewigt, T. R. Renner, R. P. Singh, M. A. Nyman, J. M. Collier, I. K. Daftari, H. Kubo, P. L. Petti, L. J. Verhey, J. R. Castro, J. R. Alonso, "Performance Specifications for Proton Medical Facility," March 1993, LBL-33749.
2. Verhey L (Chairman), Blattman H, DeLuca PM, Miller D. Clinical Proton Dosimetry Part I: Beam Production, Beam Delivery and Measurement of Absorbed Dose. Report 59 of the International Commission on Radiation Units and Measurements, Bethesda, MD, 53 pages, 1999.

Solicited, Expert Review Articles

1. Verhey LJ. Immobilizing and Positioning Patients for Radiotherapy. Sem. in Rad. Onc. 5(2): 100-114, 1995.
2. Verhey LJ, Smith V. The Physics of Radiosurgery. Sem. in Rad. Onc. 5(3): 175-191, 1995.
3. Verhey LJ. 3-D Conformal Therapy Using Beam Intensity Modulation. Front. Radiat. Ther. Oncol. 29: 139-155, 1995.
4. Verhey LJ. Conformal Therapy Using Proton Beams. in 3D Radiation Treatment Planning and Conformal Therapy, Purdy JA and Emami B, eds., Medical Physics Publishing, Madison, WI, pp. 33-38, 1995.
5. Verhey, LJ. Comparison of Three-dimensional Conformal Radiation Therapy and Intensity-Modulated Radiation Therapy Systems. Sem. in Rad. Onc. 9(1): 78-98, 1999.
6. Verhey LJ. Comparison of 3-D Conformal Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) Systems. Sem. in Rad. Onc. 9(1): 78-98, 1999. Verhey LJ. Issues in Optimization for Planning of Intensity-Modulated Radiation Therapy. Sem. In Rad. Onc. 12(3): 210-218, 2002.
7. Verhey LJ. Book Review: A brief history of the Harvard University cyclotrons by Richard Wilson. Accepted for publication in Int J Radiat Oncol Biol Phys 2004.

Non-Refereed Articles

1. Suit HD, Urano M, Goitein M, Verhey L. Biological properties of protons. Proceedings of the Sixth International Congress of Radiation Research, Tokyo, Japan 1979; 771-778.
2. Munzenrider JE, Verhey L, Doucette J. A critical appraisal of the value of CT to the radiotherapist -the abdomen. In: Husband J Ed. Proceedings of the Second European Seminar on Computed Tomography in Oncology. Edinburgh: Churchill-Livingstone, 1980; 117-133.
3. Verhey L, Goitein M. Problems of Inhomogeneities in Particle Beam Therapy. Proceedings of the International Workshop on Pion and Heavy Ion Radiotherapy: Pre-Clinical and Clinical Studies. (1981: Vancouver, British Columbia); Elsevier Science, New York, 1982; 159-169.
4. Verhey L, Munzenrider JE. Proton beam therapy. Ann. Rev. Biophys. Bioeng. 1982; 11:331-357
5. Shipley WU, Duttenhaver JR, Verhey LJ, Goitein M, Munzenrider JE, Perrone T, McNulty P, Prout GR, Suit HD. Proton radiation as boost therapy for patients with localized advanced prostatic carcinoma: a comparison with megavoltage x-rays alone. In: Rosso, R. ed. Proceedings of the International Symposium on the Management of Carcinoma of the Prostate. New York: Raven Press, 1982.
6. Munzenrider JE, Austin-Seymour M, Blitzer PJ, Gentry R, Goitein M, Gragoudas ES, Johnson K, Koehler AM, McNulty P, Moulton G, Osborne E, Seddon JM, Suit HD, Urie M, Verhey LJ, Wagner M. Proton therapy at Harvard. Strahlentherapie 1985; 161:756-763.
7. Lyman JT, Awschalom M, Berardo P, Bichsel H, Chen GTY, DiCello J, Fessenden P, Goitein M, Lam G, McDonald JC, Smith AR, TenHaken RT, Verhey L, Zink S. Protocol for heavy charged-particle therapy beam dosimetry. Report of Task Group 20, Radiation

- Therapy Committee, American Association of Physicists in Medicine, AAPM Report No. 16, 1986.
8. Fermi National Accelerator Laboratory, "Conceptual Design of a Proton Therapy Synchrotron for Loma Linda University Medical Center", June, 1986.
 9. Gragoudas ES, Seddon J, Egan K, Goitein M, Munzenrider J, Verhey L, Austin-Seymour M, Urie M, Koehler A. Present Results of Proton Beam Irradiation of Parapillary Melanomas. Retinal Diseases 2. Proceedings of Retina Workshop, Florence, Italy, 1986. Kugler Publications -Amsterdam, Berkeley/Ghedini Editore, Milano. 1987; 379-384.
 10. Gragoudas ES, Seddon J, Egan K, Goitein M, Munzenrider J, Verhey L, Austin-Seymour M, Urie M, Koehler A. Present Results of Proton Beam Irradiation of Uveal Melanomas. Acta XXV Concilium Opthal. Proceedings of XXVth Intern. Cong. of Opthal., Rome, 1986; 911-916. Kugler & Ghedini, Amsterdam, Berkeley, Milano. 1987.
 11. Verhey LJ., editor. Report of the Facilities Working Group of PTCOG, September, 1987.
 12. Verhey. LJ, Proton Beam Radiotherapy In Encyclopedia of Medical Devices and Instrumentation, Vol. 4, J.G. Webster ed. John Wiley & Sons, New York, 1988; 2358-2368.
 13. Munzenrider JE, Austin-Seymour MM, Suit HD, Verhey LJ. Heavy Particle Radiation Therapy. In Clinical Radiation Oncology Indications, Techniques, and Results, C. C. Wang, ed. PSG Publishing Company, Littleton, MA, 1988; 411-432.
 14. Verhey LJ. Proton Dosimetry as Practiced in the United States. Proceedings of the NIRS International Workshop on Heavy Charged Particle Therapy and Related Subjects held July 4 and 5, 1991 in Chiba, Japan Report NIRS-M-81, 151-158.
 15. Chu WT, Staples JW, Ludewigt BA, Renner TR, Singh RP, Nyman MA, Collier JM, Daftari IK, Kubo H, Petti PL, Verhey LJ, Castro JR, and Alonso JR. Performance Specifications for Proton Medical Facility. LBL-33749 (1993).
 16. Smith V, Verhey L, Wara W, Harsh G, Larson, D: Gamma Plan Beta Test Site Report. Stereotactic and Functional Neurosurgery 61 Suppl. 1, pp 116-123,1993.
 17. Smith V, Verhey L, Jones E, Lyman J: Consequences to the Patient in the Event of Hydraulic Unit Failure. Stereotactic and Functional Neurosurgery 61 Suppl. 1, pp 173-177, 1993.
 18. Wara W, Harsh G, Albright N, Bahary J-P, Sneed P, Smith V, Verhey L, Gutin P, Edwards M, Larson D: Dose Distribution From Stereotactic Radiosurgery of the Brain. Stereotactic and Functional Neurosurgery 61 Suppl. 1, 1993.
 19. Verhey LJ. Conformal Therapy Using Proton Beams in 3-D Radiation Treatment Planning and Conformal Therapy; Proceedings of an International Symposium, Purdy JA and Emami B, eds. Medical Physics Publishing, Madison, WI, pp 33-37, 1995.
 20. Verhey LJ, DeLuca P, Wambersie A, Whitmore GF. New ICRU Report on Proton Dosimetry in ICRU News, International Commission on Radiation Units and Measurements, Bethesda, MD, pp 9-11, December, 1995.
 21. Verhey, LJ. Physical and Biological Comparisons of Radiosurgical Treatment Modalities in Proceedings of the 1st Professor S. Takahashi Memorial International Workshop on Three Dimensional Conformal Radiotherapy as a Final Goal, Association of Three Dimensional Conformal Radiotherapy, Nagoya, Japan, pp 45-66, 1997.
 22. Verhey LJ. Comparisons of Achievable Dose Distributions Using Gamma Knife, Protons and Intensity Modulated X-rays in Proceedings of 1st International IMRT Workshop, Sternick, N ed., Advanced Medical Publishing, Madison, WI, pp 127-141, 1997.

23. Verhey LJ. Patient Immobilization for 3DRTP and Virtual Simulation in "Clinical Implementation of 3-D Radiation Therapy", Proceedings of the 14th Annual Meeting of the American College of Medical Physics, Lake Tahoe, CA, Purdy JA and Starkschall G, eds., pp 121-144, 1997.
24. Verhey LJ, Field C. Experience in Commissioning the Helax-TMS 3D RTP System in "Clinical Implementation of 3-D Radiation Therapy", Proceedings of the 14th Annual Meeting of the American College of Medical Physics, Lake Tahoe, CA, Purdy JA and Starkschall G, eds. pp 239-247, 1997.

Chapters

1. Verhey LJ, Steinberg GK. Future Directions: Particle Beams. In Stereotactic Radiosurgery, E. Alexander, J. S. Loeffler, and L.D. Lunsford, eds. McGraw-Hill, New York, pp 229-233, 1993.
2. Verhey LJ. Chapter 6: Principles of Radiation Physics. in Textbook of Radiation Oncology, S. Leibel and T.L. Phillips, eds. W. B. Saunders, Philadelphia, pp 91-114, 1998.
3. Verhey L and Bentel G. Patient Immobilization. In The Modern Technology of Radiation Oncology, J. Van Dyk, ed. Published by Medical Physics Publishing, Madison, Wisconsin, pp 53-94, 1999.
4. Verhey LJ. Chapter 11: Patient Immobilization for ED-RTP and Virtual Simulation. In 3-D Conformal and Intensity Modulated Radiation Therapy: Physics and Clinical Applications, J.A. Purdy, W.H Grant III, J.R. Palta, E.B. Butler, C.A. Perez, eds. Advanced Medical Publishing, Madison, WI, 2001
5. Verhey LJ. Chapter 22: Commissioning and Quality Assurance of Siemens IMRT System, J.A. Purdy, W.H Grant III, J.R. Palta, E.B. Butler, C.A. Perez, eds. Advanced Medical Publishing, Madison, WI, 2001
6. Verhey LJ, Petti PL. Chapter 6: Principles of Radiation Physics. In Textbook of Radiation Oncology 2nd Edition, S. Leibel and T.L. Phillips, eds. W. B. Saunders, Philadelphia, pp 101-127, 2004
7. Xia, P, Verhey LJ. Chapter 6: Intensity-Modulated Radiation Therapy in The Modern Technology of Radiation Oncology Volume 2, J. VanDyk, ed. Medical Physics Publishing, Madison, pp 221-258, 2005
8. Verhey LJ, Chuang C, Pirzkall A: Magnetic Resonance Imaging for IMRT in IMRT Handbook: Concepts & Clinical Applications, T. Bortfeld, R. Schmidt-Ullrich, W. deNeve, eds. Springer-Verlag, Heidelberg, 2006

RECENT ABSTRACTS (LAST 5 YEARS)

1. Xia P, Pickett B, Vigneault E, Verhey LJ, Roach III M: Comparison of Intensity Modulated Treatment Plans for Multiple Dominant Intra-Prostatic Lesions of Prostate Cancer presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Phoenix, AZ, 1998
2. Verhey L: IMRT with Conventional MLCs presented at the Annual Meeting of the American Association of Physicists in Medicine, Nashville, TN, 1999
3. Xia P, Wong G, Curran B, Verhey L: Dosimetric Aspects of Intensity Modulation in Serial Tomotherapy presented at the Annual Meeting of the American Association of Physicists in Medicine, Nashville, TN, 1999

4. Svatos M, Verhey L, Steinberg T: The Use of Multiple Static Fields to Smooth MLC Field Edges presented at the Annual Meeting of the American Association of Physicists in Medicine, Nashville, TN, 1999
5. Sultanem K, Shu HK, Xia P, Akazawa C, Quivey JM, Verhey LJ, Fu KK: 3-D Intensity Modulated Radiotherapy (IMRT) in the Treatment of Nasopharyngeal Carcinoma: The UCSF Experience presented at the Annual Meeting of the American Society of Therapeutic Radiology and Oncology, San Antonio, TX, 1999
6. Wicczorek DJ, Siantar CL, Descalle MA, Verhey LJ, Roach III M: The Effect of Tissue Heterogeneities and Dose Grid Resolution on Treatment Planning Dose Calculations presented at the Annual Meeting of the American Society of Therapeutic Radiology and Oncology, San Antonio, TX, 1999
7. Pirzkall A, Carol M, Pickett B, Roach III M, Verhey L: The Effect of Beam Energy and Number of Fields on Photon-Based IMRT for Deep Seated Targets presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
8. Xia P, Wong G, Somers J, Verhey L: Dosimetric Considerations in Step and Shoot IMRT Delivery presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
9. Verhey L: IMRT with Conventional MLCs presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
10. Smith V, Verhey L, Petti P: Comparison of 80% vs 50% Radiosurgery Dose Prescription Based on Biological Modeling presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
11. Graves E, Nelson S, Day M, Verhey L, Dillon W: Integration of Radiology and Radiation Oncology Data for Improved Clinical Management of Brain Tumor Patients presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
12. Descalle M, Chuang C, Daly T, Garrett D, Siantar CH, House R, May S, Patterson R, Walling R, Verhey L: Comparison of Portal Images and Images Simulated with Monte Carlo Methods presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
13. Svatos M, Rosenman J, Cullip T, Verhey L, Hughes J: Mixing Electrons with Intensity Modulated Photon Beams to Reduce Integral Dose presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
14. Chuang C, Xia P, Nguyen-Tan F, Fu K, Verhey L: Investigation of the Uncertainties in Patient Positioning and Patient Motion in IMRT Treatment presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
15. Descalle M, Wicczorek D, Daly T, Garrett D, Siantar CH, House R, May S, Patterson R, Walling R, Verhey L: Effects of Resolution and Statistical Noise on Monte Carlo Simulations of Radiation Therapy presented at the Annual Meeting of the American Association of Physicists in Medicine, Chicago, IL, 2000
16. Svatos MM, Rosenman JG, Verhey LJ: Effectiveness of Mixing Electrons with Intensity Modulated Photons for Reduction of Integral Dose for a Variety of Tumor Sizes and Depths presented at the Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Boston, MA, 2000
17. Lee JS, Verhey LJ, Smith V, Petti PL, Lamborn KR, Larson DA, Wara WM, McDermott M, Sneed PK: Quantitative Description of Dose Conformality Achieved by Gamma Knife Radiosurgery Compared to Linac Radiosurgery presented at the Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Boston, MA, 2000

18. Pirzkall A, Larson DA, McKnight TR, Graves EE, Nelson SJ, Verhey LJ: MR-Spectroscopy Results in Improved Target Delineation for High-Grade Gliomas presented at the Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Boston, MA, 2000
19. Pouliot J, Aubin M, Chuang C, Pickett B, Roach III M, Verhey L: Clinical Use of an A-Si Flat Panel for Megavoltage Portal Imaging at UCSF presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
20. Verhey L: IMRT with Multileaf Collimators presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
21. Walling R, Daly T, Siantar CH, Faddegon B, Bielajew A, Chuang C, Verhey L: Dosimetric Accuracy of the PEREGRINE Monte Carlo Dose Calculation System for Photon Beams presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
22. Chuang C, Wang L, Verhey L, Xia P: Investigation of the Use of MOSFET for Routine Clinical Dosimetric Verification presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
23. Pirzkall A, Smith V, Hoess A, Lohr F, Sneed P, Larson D, Verhey L: Radiosurgery with Gamma Knife (GK) or Linac Based Micro-MLC (mMLC) for Irregular Targets: Evaluation of Physical Dose Characteristics presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
24. Smith V, Pirzkall A, Hoess A, Lohr F, Sneed P, Larson D, Verhey L: Radiosurgery with Gamma Knife (GK) or Linac Based Micro-MLC (mMLC) for Irregular Targets: Evaluation Based on Complication and Control Probabilities presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
25. Hwang A, Verhey L, Xia P: Using a Leaf Sequencing Algorithm to Enlarge Treatment Field Length in IMRT presented at the Annual Meeting of the American Association of Physicists in Medicine, Salt Lake City, UT, 2001
26. Poon I, Lee N, Akazawa P, Quivey JM, Verhey L, Xia P: Optimal dose/volume constraints of sensitive structures in inverse planning for nasopharyngeal carcinoma presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, San Francisco, CA, 2001
27. Nakamura JL, Pirzkall A, Carol M, Xia P, Smith V, Wara WM, Petti PL, Verhey LJ, Sneed PK: Comparison of intensity modulated radiosurgery to Gamma Knife for challenging skull base lesions presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, San Francisco, CA, 2001
28. Pirzkall A, Takahashi M, McKnight TR, Graves EE, Nelson SJ, Verhey LJ, Larson DA, Sneed PK: Metabolic imaging by means of 3D MR-Spectroscopy for low-grade gliomas presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, San Francisco, CA, 2001
29. Xia P, Chuang C, Akazawa P, Phillips TL, Quivey JM, Verhey L, Lee N: Methods of reducing skin toxicity due to extended-field intensity-modulated radiation therapy (EF-IMRT) for the treatment of head and neck cancers presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, San Francisco, CA, 2001
30. Pouliot J, Aubin M, Verhey L, Bani-Hashemi A, Mitschke M, Hernandez P, Hughes J: Low dose megavoltage CT cone beam reconstruction for patient alignment presented at the Annual Meeting of the American Association of Physicists in Medicine, Montreal, Quebec, 2002

31. Chuang C, Woodruff D, Verhey L, Xia P: Investigation of the dosimetric consequences of leaf setting uncertainties for a double-focused MLC in IMRT delivery presented at the Annual Meeting of the American Association of Physicists in Medicine, Montreal, Quebec, 2002
32. Xia P, Yu N, Xing L, Verhey L: Investigation of a variable power objective function for inverse planning optimization in IMRT presented at the Annual Meeting of the American Association of Physicists in Medicine, Montreal, Quebec, 2002
33. Langen K, Pouliot J, Anezinos C, Aubin M, Hsu I, Gottschalk A, Lowther D, Shinohara K, Verhey L, Roach M: Inter-user variability of the BAT ultrasound system presented at the Annual Meeting of the American Association of Physicists in Medicine, Montreal, Quebec, 2002
34. Pirzkall A, Li X, Larson DA, Verhey LJ, Nelson SJ: MR-spectroscopy imaging for resected high-grade gliomas prior to radiation therapy: Tumor extent according to metabolic activity in relation to MRI presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, 2002
35. Xia P, Liu Y, Poon I, Akazawa P, Quivey J, Verhey LJ, Lee N: Development of a standard set of dose constraints to sensitive structures in treatment of nasopharyngeal cancers using inverse planned IMRT presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, 2002
36. Chuang C, Xia P, Akazawa P, Verhey L, Quivey JM, Lee N: Comparison of three treatment techniques involving IMRT fields for head and neck cancers presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, 2002
37. Langen K, Pouliot J, Anezinos C, Aubin M, Gottschalk AR, Hsu I, Lowther D, Shinohara K, Weinberg V, Verhey LJ, Roach M: Evaluation of the use of the BAT ultrasound system for prostate localization and repositioning: an inter-user study presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, 2002
38. Akazawa C, Akazawa P, Lee N, Quivey J, Verhey L, Xia P: Forward-planned treatment techniques using multisegments for head and neck cancer presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, New Orleans, LA, 2002
39. Pouliot J, Xia P, Aubin M, Verhey L, Langen K, Bani-Hashemi A, Svatos M, Ghelmansarai F, Mitschke M: Dose-guided radiation therapy using low-dose megavoltage cone-beam CT presented at the Annual Meeting of the American Association of Physicists in Medicine, San Diego, CA, 2003
40. Chuang C, Curran B, Verhey L: Clinical implementation and validation of a commercial Monte Carlo dose calculation system presented at the Annual Meeting of the American Association of Physicists in Medicine, San Diego, CA, 2003
41. Lee M, Pirzkall A, Akazawa P, Verhey LJ, Nelson SJ: MR Spectroscopy of radiation effects in healthy brain tissue following radiotherapy presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, 2003
42. Pouliot J, Xia P, Aubin M, Verhey L, Bani-Hashemi A, Ghelmansarai F, Mitschke M, Svatos M: Low-dose megavoltage cone-beam CT for dose-guided radiation therapy presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, 2003
43. Lee N, Zhu N, Baker L, Shin EJ, Quivey JM, Phillips TL, Verhey L, Xia P: Intra-fraction patient motion in head/neck cancer patients undergoing intensity-modulated radiation therapy (IMRT) presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, 2003

44. Park C, Lee N, Kim Y, Quivey JM, Phillips TL, Verhey LJ, Xia P: A method to account for dose fractionation by using a modified equivalent uniform dose algorithm presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, 2003
45. Aubin M, Roach M, Verhey L, Pouliot J: Clinical acceptance of the flat panel for megavoltage portal imaging at UCSF: Three year experience presented at the Annual Meeting of the American Association of Physicists in Medicine, Pittsburgh, PA, 2004
46. Aubin M, Pouliot J, Milender L, Shinohara, K, Pickett B, Anezinos C, Verhey L, Roach M: Daily prostate targeting with implanted gold markers and an a-Si flat panel EPID at UCSF: A Five year clinical experience presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Atlanta, GA, 2004
47. Lometti M, Thurston D, Aubin M, Verhey L, Lockhart JM, Bland R, Roach M, Pouliot J: Are lateral electronic portal images adequate on-line daily targeting of the prostate? Results of a prospective study presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Atlanta, GA, 2004
48. Chen H, Xia P, Verhey L, Roach III M: Dosimetric consequences to the pelvic lymph nodes due to the daily motion of the prostate presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Atlanta, GA, 2004
49. Xia P, Hsu I-C, Speight J, Zytkevich A, Gottschalk A, Verhey L: Two isocenter treatment technique for pelvic malignancies with positive pelvic and para-aortic lymph nodes using intensity modulated fields presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Atlanta, GA, 2004
50. Gao M, Perks JR, Kubo HD, Luo C, Skubic SE, Verhey LJ, Smith V, Goetsch SJ, Araki F: The application of newly developed glass rod dosimeter in the quality assurance and dosimetric audit of Gamma Knife presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Atlanta, GA, 2004

RESEARCH PROGRAM

FIVE SIGNIFICANT RECENT PUBLICATIONS:

1. Xia P, Verhey LJ. MLC leaf sequencing algorithm for intensity modulated beams with multiple static segments. Medical Physics 25(8): 1424-1434, 1998

As senior author, I worked closely with Dr. Xia to develop the most efficient general method of leaf segmentation for intensity modulated radiotherapy. This method has been generally accepted by other investigators in the field as the gold standard of leaf segmentation algorithms.

2. Graves EE, Pirzkall A, Nelson SJ, Verhey LJ, Larson DA: Registration of magnetic resonance spectroscopic imaging to computed tomography for radiotherapy treatment planning. Med. Phys. 28(12): 2489-2496, 2001

As senior technical author, I developed the data transfer and data verification system for overlaying the Gamma Knife dose distributions from the planning system on the MRSI images as required for accurate correlation of clinical outcome with radiosurgery dose.

3. Xia P, Hwang AB, Verhey LJ: A leaf sequencing algorithm to enlarge treatment field length in IMRT. Med. Phys. 29(6): 991-998, 2002

As senior author, I provided the technical guidance to fully understand the problems with the clinical leaf sequencing algorithm and to devise a method to avoid undeliverable sequences through the development of a new computer algorithm.

4. Langen KM, Pouliot J, Anezinos C, Aubin M, Gottschalk AR, Hsu I-C, Lowther D, Liu Y-M, Shinohara K, Verhey LJ, Weinberg V, Roach III M: Evaluation of ultrasound-based prostate localization for image-guided radiotherapy. Int J Radiat Oncol Biol Phys. 57(3): 635-644, 2003

As senior technical author, I was heavily involved in the design of the experimental questions and the analysis and interpretation of the data that made this highly controversial and important paper publishable. This study was seminal in showing the superior accuracy of direct radiographic visualization of radiopaque markers in the prostate compared to ultrasound localization.

5. Xia P, Lee N, Liu YM, Poon I, Weinberg V, Shin E, Quivey JM, Verhey LJ: A study of planning dose constraints for treatment of nasopharyngeal carcinoma using a commercial inverse treatment planning system. Int J Radiat Oncol Biol Phys 59(3): 886-896, 2004

As senior author, I provided guidance, technical advice and encouragement as well as diplomatic editing that were needed to get this excellent paper published. This paper describes the ultimate method of efficient inverse planning of tumors of the head and neck with intensity modulated radiotherapy (IMRT) and has been responsible for making IMRT of head and neck lesions available to a larger fraction of patients.

CURRENT RESEARCH INTERESTS

1. Precision Radiotherapy.

I am working to improve the applicability, efficiency and safety of intensity modulated x-ray beam treatments (IMRT), planned either with conventional 3DCRT planning programs or inverse treatment planning programs. I have developed collaborations between UCSF and the vendors of these planning programs (NOMOS, Philips) and delivery systems (Siemens) through which we are optimizing the clinical use of IMRT.

Precision treatments require accurate positioning of patient anatomy and accurate localization of the target within the patient on a daily basis. New methods of patient immobilization, position verification and target localization are being developed. The locations of imbedded radiopaque markers are being routinely detected on a daily basis with electronic portal imagers and manually compared with calculated positions from the treatment plan prior to treatment. Work is underway to automate the detection, comparison and required couch motions to allow precise daily positioning of prostate tumors.

The next challenge in positioning is accurate dose delivery to targets that move with respiration. I am establishing a collaboration with a vendor that manufactures implantable radiofrequency transmitters that can be stimulated by external antennas and located by triangulation in real time. I am interested in using this information to move the patient couch or the beam-defining collimator leaves, to keep the target at the treatment isocenter during all phases of the respiratory cycle.

2. Image- and dose-guided radiotherapy

In collaboration with Siemens, we are pursuing the acquisition and manipulation of reconstructed 3D images using a series of images taken rapidly with an electronic portal imager at different gantry angles. These images can be compared with the treatment planning CT on a daily or weekly basis for patient position verification. These 3D images can also be used as a basis for daily analysis of delivered dose. I am working with other faculty and graduate students to develop a method of using this information in an efficient manner to improve the quality of the dose actually delivered to each patient by adjusting treatment plans during a course of treatment if the daily imaging proves that it is necessary.

3. Functional imaging to assist tumor identification.

I am working with other faculty in Radiation Oncology and Radiology to evaluate the use of biological information in the definition of tumor for radiotherapy targeting. Magnetic Resonance Spectroscopy (MRSI) is proving very useful in defining areas of active tumor in prostate and brain. In addition, a state-of-the-art PET-CT scanner is being installed at UCSF in China Basin before the end of 2004. This unit will have the highest spatial resolution currently available for PET information and promises to be extremely helpful in identifying active areas of tumor, particularly for patients with head and neck lesions. I am working to find the best method of transferring and displaying this information for Radiation Oncologists and in evaluating the impact of both PET-CT and MRSI technologies on tumor control.

Exhibit C

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Telephone: (415) 848-4900

**Attorneys for Defendants CYTYC CORPORATION and
CYTYC SURGICAL PRODUCTS II, INC.**

**Declaration of Lynn J. Verhey, Ph.D.
Case No. C05-05312 RMW**

1 My name is Lynn J. Verhey. I am a resident of the state of California and am over the age of
2 18. I am presently employed by the University of California, San Francisco as a Full Professor and
3 serving as Vice-Chair in the Department of Radiation Oncology. I make the following declaration
4 based on my personal knowledge, training and experience, and if called upon to testify, I could and
5 would testify competently to the matters set forth below.

6 **I. INTRODUCTION AND MY EXPERT QUALIFICATIONS**

7 I received my B.A. in Physics from Kalamazoo College, Kalamazoo, Michigan in 1962, and
8 my M.S. and Ph.D. in Physics in 1964 and 1968, respectively, from the University of Illinois, Urbana,
9 Illinois. The subject of my research during my education was on the decays of certain charged
10 particles produced by high energy interactions of protons with Hydrogen and Deuterium.

11 I took a position at UCLA and served as a post-doctoral researcher and Assistant Professor of
12 Physics from 1968-70, doing experiments at Lawrence Berkeley Laboratory and teaching physics to
13 undergraduate physics students. I moved to Harvard University in 1970 as an Assistant Professor,
14 continuing to teach undergraduate physics and perform high energy experiments, this time at Fermi
15 National Accelerator Laboratory in Illinois. In 1975 I took a position as Hospital Radiation Physicist
16 at Massachusetts General Hospital (MGH) with a concurrent continuing position as Assistant Professor
17 at the Harvard Medical School. I then worked with the MGH group to develop and implement proton
18 radiation therapy as an alternative to x-ray therapy. In 1990, I took the position as Chief of the Physics
19 Division and Associate Professor in the Department of Radiation Oncology at UCSF. Since that time,
20 I have continued to serve as Chief of the Physics Division and, in addition, as Vice-Chair of the
21 Department and as a Full Professor.

22 As part of my responsibilities at UCSF, I have mentored numerous graduate and post-graduate
23 students, taught an undergraduate class in the Department of Nuclear Engineering at the University of
24 California, Berkeley (UCB) and graduate classes in the Department of Bioengineering at UCB as well
25 as at UCSF. I have taught medical physics to medical residents at UCSF as well as to physics
26 residents. I have performed research on new methods of delivering radiation to cancer patients and
27 have published over 100 technical papers in this field. I was certified as a therapeutic radiological
28 physicist by the American Board of Radiology in 1982, appointed a fellow of the American

1 Association of Physicists in Medicine in 2002 and a fellow of the American Society of Therapeutic
2 Radiology and Oncology in 2006.

3 I am a well-recognized expert in methods of delivering radiation to cancer patients, having
4 given numerous scientific lectures at scientific meetings, both nationally and internationally. I am
5 attaching a current copy of my curriculum vitae to this declaration.

6 **II. TOPICS THAT I HAVE BEEN ASKED TO ADDRESS**

7 I have been asked by counsel for Cytoc Corporation and Cytoc Surgical Products, Inc. to
8 provide expert testimony relating to United States Patent Nos. 5,913,813 (the "813 patent") and
9 6,413,204 (the "204 patent"), which are the patents of issue in this lawsuit. The 813 patent describes
10 and claims an invention in the field of a balloon catheter for treatment of proliferative tissue, while the
11 204 patent extends this concept to describe and claim as an invention a method for treatment of
12 proliferative tissue diseases using an interstitial brachytherapy apparatus. These patents describe a
13 catheter which can be used with an array of radiation-producing materials to irradiate the wall of a
14 surgical cavity and a defined thickness of tissue beyond that wall, to doses that can both avoid necrosis
15 of normal tissue and destroy cancer cells that might populate the area. In the case of both the 813 204
16 patents, I have been asked to provide testimony with respect to the knowledge of people of ordinary
17 skill in the relevant art and in particular, at the time the described inventions were made, which I
18 understand to be in the time frame of 1997 to 1999, based on their respective filing dates. I have also
19 been asked to provide an opinion of how one of ordinary skill in the art would interpret elements of the
20 claims of the 813 and 204 patents which cover the inventions at issue. I can also provide testimony on
21 any other background information or technical issue on these patents that the Court may request.

22 **III. INFORMATION CONSIDERED IN FORMING MY OPINIONS**

23 In forming the opinions stated in this declaration, I have reviewed and considered the text of
24 the 813 patent and the patent history associated with the issuance of the patent as well as the text of the
25 204 patent and the history associated with its issuance. I have also considered the preliminary claim
26 construction and identification of extrinsic evidence exchanged by both parties. I have also reviewed
27 information in "The Physics of Radiation Therapy" (2d edition, 1994) by Faiz Khan, PhD, published
28 by Williams and Wilkins. I have not reviewed any written or oral opinions from any expert whom

Xoft Microtube has retained or may retain in connection with the 813 and 204 patents and I reserve the right to modify my opinions stated in this declaration after having reviewed any such opinion offered by any such expert. I also reserve the right to modify my opinions based on any rulings that the Court might issue in the future relating to these patents.

IV. APPROACH I HAVE USED IN READING THE 813 AND 204 PATENTS AND INTERPRETING THEIR CLAIMS

I understand that the claims of the 813 patent at issue in this lawsuit are claims 1, 2, 3, 4, 8 and 12 found in columns 4, 5 and 6 of the patent. I also understand that the claims of the 204 patent at issue in this lawsuit are claims 1, 2, 3, 4, 8, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 30, 32, 34, 35 and 36 found in columns 8, 9, 10, 11 and 12 of the patent. In the case of patent 813, the claims relate specifically to subject matter described in columns 1-4, beginning with a summary of the invention and Figures 1-5, and for patent 204, the claims relate specifically to the discussion in columns 2-8, beginning with a summary of the invention and Figures 1-7. I understand that a patent claim must be interpreted in light of the specification of the invention and the illustrative figures which are intended to describe the invention that is being claimed.

I also understand that a claim is to be interpreted from the standpoint of one of ordinary skill in the art, at the time of the invention, which is approximately when a patent application first describing the invention was filed. Based on the respective filing dates of the patent applications, I understand the relevant time frame to be between 1997 and 1999.

I understand that patents 813 and 204 can be considered to have a "parent-child" relationship. Indeed, many of the claims of 204 specifically relate to the same subject matter described in columns 1-4 and figures 1-5 of patent 813. I understand that the proper interpretation of the claims of the 813 and 204 patents also requires analyzing the prosecution history of these two patents, i.e., the public record of the communications exchanged between the applicants and the United States Patent and Trademark Office (PTO) leading up to the issuance of the 813 and 204 patents, respectively.

In understanding and interpreting the claims of the 813 and 204 patents, I have focused on the specifications and drawing figures in the patents, and the prosecution histories of the 813 and 204 patents. I have read these materials as one of ordinary skill in the art would have read them in the

1 period 1997 to 1999. When appropriate, I have consulted a contemporary reference textbook, which
2 can be helpful in understanding the meaning of a claim term, particularly if the meaning remains
3 unclear after reading the specifications and the prosecution histories.

4 I understand that claim terms are normally used consistently throughout a patent. One has to
5 assign meaning to each and every term in a claim.

6 **V. LEVEL OF SKILL OF ONE OF ORDINARY SKILL IN THE ART**

7 For purposes of interpreting the claims of the 813 and 204 patents, the relevant scientific area is
8 radiation oncology physics, with a focus on brachytherapy. Typically, individuals of ordinary skill in
9 this field would hold a M.S. degree in Physics or Engineering, with 3 or more years of clinical medical
10 physics experience; or a Ph.D. degree in Physics or Medical Physics with 2 or more years of clinical
11 experience.

12 Such a person would have a broad knowledge of the physics of brachytherapy procedures, of
13 the principles of radioactivity and an understanding of the effects of radiation on cells. In addition,
14 such a person would have an understanding of other means of treating cancer cells with radiation such
15 as an external, gantry-mounted linear accelerator. Individuals with such qualifications are considered
16 eligible for certification as a radiation oncology physicist by entities such as the American Board of
17 Radiology and considered capable of working independently in a clinical environment as a medical
18 physicist.

19 **VI. OVERVIEW OF THE INVENTIONS DESCRIBED IN THE 813 AND 204 PATENTS**

20 The claims of the 813 patent relate to the description of an instrument comprising a concentric
21 arrangement of an inner spatial volume and an outer spatial volume defined by an inflatable chamber,
22 disposed near the distal end of a catheter body where one of the volumes can contain a source of
23 radiation, while the other volume would normally contain a radiation absorptive material. In the
24 preferred embodiment, shown in Figure 1 of the patent, the inner volume is an inflatable chamber
25 concentric with the catheter body containing a radioactive source. The outer chamber, concentric with
26 the inner volume, is then inflated with air or other radiation absorbing material, resulting in the wall of
27 the outer chamber being in contact with the outer surface of the surgical cavity at all points. The
28 distance between the radiation source and the wall of the outer chamber can be made constant. This

embodiment permits the delivery of radiation to a ring of tissue outside a surgical cavity that is judged to possibly include cancer cells, and by manipulating the volume and material in the outer chamber, the ratio of the dose to the surface of the surgical cavity to the dose at the tissue depth where the minimum dose is prescribed to be received, can be controlled to maximize the effectiveness of the treatment. An effective treatment could be defined as one that delivers the prescribed dose to the tissue at the depth of interest, and a dose to tissue between the wall of the surgical cavity and the prescription depth which is higher, but not likely to necrose healthy tissue.

The 813 patent teaches that other embodiments can be used to deliver radiation to proliferative tissue outside a surgical cavity and these are discussed in 2:64 – 4:20 and supported by figures 3-5. These other embodiments include the use of a radioactive liquid in an inner inflatable chamber, or a plurality of radioactive solid particles, a slurry of a fluid containing particles of a radioactive isotope or a solid radioactive source. In addition, these same radioactive sources can be placed in the space between the inner inflatable chamber and the outer inflatable chamber. Any of these embodiments might be used as a means of delivering radiation to a ring of tissue outside the wall of a surgical cavity.

The 204 patent, which is a continuation-in-part of the 813 patent, describes an apparatus for brachytherapy and a method for using it for interstitial delivery of radiation to tissue proximate to the cavity formed by surgical removal of proliferative tissue. The apparatus includes a catheter body member having a proximal end and a distal end, an inner spatial volume proximate to the distal end of the catheter body member, an outer spatial volume defined by an expandable surface element proximate to the distal end of the body member and surrounding and concentric with the inner spatial volume. In the usual embodiment of the device, a radiation source is disposed in the inner spatial volume.

The 204 patent describes a number of embodiments that can be used with the device for delivery of radiation, including radioactive microspheres (Fig. 4), concentric non-spherical chambers (Fig. 5), a single solid radiation emitting material inside the catheter and an expandable cage defining the shape of the cavity (Fig. 6), a radioactive fluid filling the outer chamber (Fig. 7a), a radioactive fluid filling the inner chamber and the outer chamber filled with air or other radiation absorbing substance (Fig. 7b), and a single solid source in the catheter, surrounded by the outer chamber filled

1 with radiation absorbing substance (Fig. 7c). Figure 7d shows examples of radiation profiles which
2 might be obtained by the embodiments shown in Fig. 7a – 7c where the depth of interest is shown as 2
3 cm from the surface of the outer volume. As can be seen, different embodiments can be used to vary
4 the ratio of the dose at the prescription depth, to the dose at the surface of the cavity.

5 **VII. THE MEANING OF THE DISPUTED CLAIM TERMS IN THE 813 AND 204**
6 **PATENTS TO ONE OF ORDINARY SKILL IN THE ART**

7 I have reviewed and relied upon the material listed in Section III above. Based upon these
8 materials, my own knowledge of the technical field to which the patented inventions relate, and my
9 familiarity with the level of ordinary skill in the art around the time that the 813 and 204 patents were
10 filed, I have formed opinions as to how one of ordinary skill in the art would have interpreted certain
11 claim terms at the time of the invention. My opinion of the meaning of each of these disputed terms is
12 set forth below. I have referenced the materials listed in Section III upon which I have relied for these
13 opinions. In situations where the disputed claim term is present in both patents 813 and 204, my
14 interpretation of the term is given only once. The list of disputed claim terms includes those identified
15 by either party in the case.

16
17 Radionuclide(s) – any radioactive isotope that is unstable and thereby decays into a different
18 isotope with the emission of radiation (Physics of Radiation Therapy”, p.12, see 813 2:50 – 2:55 for
19 examples).

20
21 Means for rendering uniform the radial dose profile –the radial dose profile is defined as the
22 absorbed dose to tissue as a function of distance from the center of the cavity along a particular
23 direction of interest. As described in the 813 patent, the points of interest in this profile would be from
24 the wall of the surgical cavity to a depth somewhat beyond that at which the prescription is defined.
25 The device provides a means for modifying the ratio of the dose at the depth of interest to the dose at
26 the surface of the cavity as desired for the particular clinical application, through manipulation of the
27 quantity and type of substances contained in the spatial volumes as shown in patent 813 Fig. 4 , also
28 1:59-67.

1
2 Predetermined constant spacing – the spacing between the inner spatial volume and the wall of
3 the outer inflatable chamber can be made constant in all directions if the outer chamber is spherical
4 (Fig. 1 of 813), or constant along a radial direction if non-spherical (see Fig. 3 of 813 and 3:10-13),
5 whenever the outer chamber is inflated.

6
7 Outer closed inflatable chamber – this is a balloon or cage or inflatable chamber of any type
8 that can be made to be in contact with the surface of the surgical cavity when the catheter has been
9 inserted and the chamber is inflated (see 813 2:38-41).

10
11 Inner spatial volume – a region of space which is surrounded by the outer spatial volume
12 defined by a closed inflatable chamber. As shown in Fig. 1 of 813, it can be defined by the wall of an
13 inflatable chamber (see 2:34-36 of 813). As shown in Fig. 5 of 813 and 2:56-67 of patent 813, it can be
14 defined as the region of space containing a radiation source or an array of radiation sources. This is
15 also described in patent 204 2:56-60, 3:58-59, 4:4-7, 4:44-48 and 5:1-6.

16
17 The radioactive material – referred to in claim 8 in 813, this refers to any material containing
18 radionuclides, including microspheres, radioactive fluid or individual solid radioactive particle(s) that
19 can be enclosed in either of the spatial volumes. See patent 813 2:51-67 and 4:46-47.

20
21 Outer spatial volume – a region of space defined by an expandable surface element surrounding
22 an inner spatial volume (see patent 204 2:60-63, 4:4-5 and 8:22-23).

23
24 Brachytherapy – a method of treatment in which radioactive sources are used to deliver
25 radiation at a short distance by interstitial, intracavitary, or surface application (see “The Physics of
26 Radiation Therapy”, p. 418). As used in patent 204, 1:31 – 1:34, it is defined as radiation therapy
27 delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other
28 proliferative tissue disease site

1
2 Intraoperatively – this refers to the fact that the interstitial brachytherapy apparatus is placed
3 into the surgical resection cavity during the operation – i.e., after surgical removal of tumor, but prior
4 to closing the surgical site as indicated in patent 204 7:58 – 7:60.

5
6 Expandable surface element – an expandable or inflatable device such as a balloon or cage that
7 can be expanded or inflated in order to contact the inner surface of the surgical resection cavity (see
8 patent 204 2:61-63).

9
10 Radiation source – any device or material capable of generating radiation, such as radionuclides
11 or a high voltage electronic tube that can produce accelerated electrons which can be used directly to
12 irradiate cells or to produce x-rays through the interaction of these accelerated electrons with a target
13 (see patent 204 1:27-30, 1:47-50, 2:45-46 and 4:10-14).

14
15 Isodose profile – this would usually be a description of the dose received by points in tissue–
16 for example, a plot of dose vs. distance from the center of a source, or plurality of sources. As used in
17 5:12 – 5:41 in patent 204, it refers to 3-dimensional surfaces on which all points receive the same dose.

18
19 Surgical resection – surgical removal of tissue from the body (see patent 204 7:55-58).

20
21 Minimum prescribed dose – the minimum dose needed to destroy existing cancer cells in the
22 opinion of the physician (see line 52 in Fig.7d of patent 204).

23
24 Configuring the inner and outer spatial volumes to provide minimum prescribed absorbed dose
25 – as defined in claims 1, 19 and 32 of patent 204, where the radioactive material is disposed in the
26 inner spatial volume, the rate at which the dose falls off between the surface of the surgical cavity and
27 the depth at which the minimum dose is to be prescribed, can be controlled by modifying the quantity
28 and type of radiation absorbing material contained within the outer spatial volume. The safe delivery

1 of the minimum prescribed dose at the depth of interest requires that the tissue intervening between the
2 surface of the cavity and the depth of interest receives a dose which is equal to, or greater than the
3 prescribed dose but less than that which would necrose (i.e., lethally damage) healthy tissue. See
4 patent 204 5:22-41 and 6:16 - 7:28.

5
6 Minimum distance outward from the outer spatial volume expandable surface – the target tissue
7 is defined as that tissue which is between the surface of the inflated outer spatial volume and a
8 minimum distance outward from that surface, determined by the physician, to include the region in
9 which tumor cells might reside (see patent 204 6:16-22 and Fig. 7d).

10
11 Providing a controlled dose at the outer spatial volume expandable surface to reduce or prevent
12 necrosis in healthy tissue – by adjusting the distance between the radiation source and the surface of
13 the outer spatial volume, or by adjusting the type of radiation absorbing material in the outer spatial
14 volume, the ratio of the dose at the surface of the outer spatial volume to the dose at the depth of
15 prescription, can be controlled (see patent 204 6:42 – 7:28 and Figs. 7a – 7d).

16
17 Adapting the expandable surface to contact tissue surrounding the resection cavity to conform
18 the tissue – the volume of the expandable surface can be adjusted by inflation until the surface of the
19 expandable volume is in contact with the surface of the resection cavity at all points. In this state, the
20 shape of the resection cavity conforms to the shape of the expandable surface (see patent 204 5:47-61).

21
22 Desired shape of the expandable surface element – the desired shape of the expandable surface
23 element is that shape which provides the predetermined constant spacing between the inner spatial
24 volume and the conformed surface of the resection cavity (see patent 204 5:47-61).

25
26 Delivering a prescribed absorbed dose – once the inflated expandable surface element is in
27 contact with the surface of the surgical cavity, the dose at the prescription depth can be delivered once
28 the radiation source is introduced into the catheter (see patent 204 5:66 – 6:28).

Inner and outer volumes are configured to provide a minimum prescribed dose - see above.

Controlled dose – refers to controlling the ratio of doses at the depth of prescription to the dose at the surface of the surgical cavity. See patent 204 6:42 – 7:28 and Figs. 7a-7d which show various configurations to deliver minimum prescribed dose with variable doses to the surface of the surgical cavity.

Reduce or prevent necrosis in healthy tissue proximate to the expandable surface – by controlling the ratio of doses at the depth of prescription to the dose at the surface of the surgical cavity through the use of different amounts and types of radiation absorbers in the inner and outer expandable volumes, necrosis of healthy tissue in the vicinity of the surface of the surgical cavity can be prevented or reduced. See patent 204 6:42 – 7:28 and Figs. 7a-7d which show various configurations to deliver minimum prescribed dose while reducing or preventing necrosis in proximate healthy tissue.

Predetermined spacing – the spacing between the inner and outer spatial volumes can be set to a predetermined and constant value by modifying the level of inflation or expansion of one or both volumes (see patent 204 5:22-32).

Interstitial – pertaining to or situated in the interspaces of a tissue. These interspaces are not naturally occurring. See patent 204 1:31-34 and December 20, 2000 amendment at pages 11-15 and “The Physics of Radiation Therapy” at pages 457-458.

A plurality of radioactive solid particles placed at pre-determined locations within the inner spatial volume to provide a desired composite radiation profile – as shown in Figure 5 of patent 813, and as described in 2:64– 3:9, a plurality of radioactive particles which can be positioned in such a way as to generate a desired dose profile.

Interstitial brachytherapy – short distance radiation therapy applied directly into the interspaces of tissue in a cavity that is not naturally occurring (see “Physics of Radiation Therapy” pages 418 and 457-458).

Three-dimensional isodose profile – a three dimensional surface on which the radiation dose is the same at all points (see patent 204 5:16-19).

Solid radiation source – a radiation source that has a fixed shape and volume and is not deformable (see patent 204 4:44-48 and 4:54-56).

The prescribed absorbed dose is delivered to the target tissue in substantially three dimensions – as described in claim 18 of patent 204, this refers to the fact that, once the outer chamber is expanded, the tissue surrounding the chamber conforms to the shape of the chamber, thereby assuring that all points in tissue that are a fixed distance from the wall of the surgical cavity will receive the identical dose.

Extrinsic Evidence

The Physics of Radiation Therapy by Faiz Khan, p. 12 (radioactivity and radionuclides), p. 418 (brachytherapy), p. 457-458 (interstitial brachytherapy)

VIII. DEMONSTRATIVES

I understand that I might be requested to provide a tutorial regarding the technology of the 813 and 204 patents. I would expect to deliver this information using a combination of Powerpoint slides and photocopied material that I have used previously in the teaching of the Physics of Radiation Oncology to professionals and students.

IX. OTHER CASES IN WHICH I HAVE TESTIFIED DURING THE PAST FOUR YEARS

I have provided testimony as an expert at a deposition in the case of *Maggiani vs. University of Southern California* on February 20, 2006.

1 **X. COMPENSATION**

2 I am being compensated for my work on this matter at a rate of \$500 per hour. My
3 compensation does not depend on the outcome of this case.

4 * * *

5 I declare under penalty of perjury that the foregoing statements are true and correct.

6 Dated: October 12, 2006

San Francisco, California

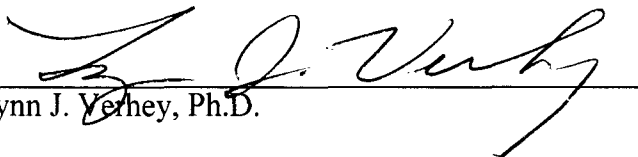
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Lynn J. Verhey, Ph.D.

EXHIBIT I

#7/A



PATENT APPLICATION

OUR FILE NO. 970344.ORI

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re App : Jeffery A. Williams, et al.
S.N. : 08/900,021 : September 1, 1998
Filed : July 24, 1997 : Art Unit 3736
For : DOUBLE WALL BALLOON CATHETER
FOR TREATMENT OF
PROLIFERATIVE TISSUE : Examiner J. Lacyk

ASSISTANT COMMISSIONER FOR PATENTS

WASHINGTON, D.C. 20231

Dear Sir:

Responsive to the first Official Action of May 12, 1998,
please amend the above-captioned application as follows:

IN THE CLAIMS:

Please cancel Claim 12.

Please amend the following claims:

1 (Amended). Apparatus for delivering radioactive
emissions to a body location with a [controlled] uniform
radiation profile, comprising:

(a) a catheter body member having a proximal end and
distal end;

(b) an inner spatial volume disposed [at] proximate
the distal end of the catheter body member;

(c) an outer, closed, [distensible] inflatable
chamber defined by a radiation transparent wall [disposed at]

A1

11

affixed to the body member proximate the distal end [of the body member] thereof in surrounding relation to the inner spatial volume with a predetermined constant spacing between said inner spatial volume and the radiation transparent wall;

AI (d) a material containing a radionuclide(s) disposed in one of the inner spatial volume and outer chamber; and

(e) means disposed in the other of the inner spatial volume and outer chamber for [controlling] rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber containing the radionuclides.

2 (Amended). The apparatus as in Claim 1 wherein said inner spatial volume is an inner closed, [distensible] chamber defined by a further radiation transparent wall.

3 (Amended). The apparatus of Claim 1 wherein the means for [controlling] rendering uniform the absorbed dose profile is a radiation attenuating material.

4 (Amended). The apparatus of Claim [2] 3 wherein the radiation [absorbing fluid] attenuating material is selected from a group consisting of barium sulphate, water, and X-ray contrast media.

AI 8 (Amended). The apparatus as in Claim [1] 2 wherein the inner chamber contains the radioactive material.

A3 10 (Amended). The apparatus as in [any one of Claims 7 or] Claim 8 wherein the radioactive material is a fluid.

11 (Amended). The apparatus as in [any one of Claims 7 or]
A4 Claim 8 wherein the radioactive material is a solid.

12, 12 (Amended). The apparatus as in Claim 1 wherein the
material containing a radionuclide comprises a plurality of
radioactive solid particles [are] placed at predetermined
A5 locations within the inner spatial volume to provide a desired
composite radiation profile.

Please add the following claim:

13, 14. The apparatus as in Claim 2 wherein the inner and outer
A6 chambers are spherical in shape and are concentric.

R E M A R K S

This Amendment is submitted in response to the first
Official Action of May 12, 1998. Reconsideration and allowance
of Claims 1-11 and 13, as presently amended, are respectfully
requested.

The present invention is directed to an apparatus for
treating proliferative tissue disorders by delivering radioactive
emissions to target tissue within the body with a uniform radial
absorbed dose profile whereby diseased tissue may be irradiated
with sufficient intensity to kill disease cells, but without
producing necrosis of neighboring healthy tissue. With the
apparatus of the present invention, it is possible to deliver a
desired radiation dose at a predetermined radial distance from a
source of radioactivity by providing a catheter body member
having an inner spatial volume disposed proximate the distal end
of the catheter body and with an outer, closed, inflatable,

chamber defined by a radiation transparent wall affixed to the body member proximate the distal end thereof in a surrounding relation to the inner spatial volume with a predetermined constant spacing between the inner spatial volume and the radiation transparent wall. A material containing a radionuclide is introduced through the catheter body in either the inner spatial volume or the outer chamber and the other of the inner spatial volume or outer chamber not containing the radionuclide is made to contain a radiation attenuating material for rendering uniform the radial absorbed dose profile of the emissions from the one of the inner spatial volume and outer chamber that contains the radionuclide.

In the Official Action, objection was raised to Claims 4 and 13 under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 13 has been amended to clarify that the material containing a radionuclide as recited in claim 1 comprises "a plurality of radioactive solid particles". Claim 4 has been amended by changing "radiation absorbing fluid" to -- radiation attenuating material --, the latter phrase finding an antecedent in Claim 3 from which it now depends.

Concerning the rejection on the merits, Claims 1-5, 8 and 10 were rejected under 35 U.S.C. §102(b) as being anticipated by Ishiwara et al. This rejection is respectfully traverse. Before it is appropriate to find a claim anticipated under 35 U.S.C. §102(b), it is necessary to find within the four corners of the prior art reference relied upon a full teaching of each and every

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element of the claims sought to be anticipated. As Claim 1 has now been amended, it calls for an outer, closed, inflatable chamber located proximate the distal end of a catheter body member in surrounding relation to an inner spatial volume such that there is a predetermined constant spacing between the inner spatial volume and the radiation transparent wall. There is then provided a means disposed in the chamber, not having the radiation source, a substance for rendering uniform the radial absorbed dose profile of the emissions from the chamber that contains the radiation source. In the Ishiwara et al. '360 patent relied upon for anticipation, the outer chamber defined by the radiation transparent wall 12 cannot provide a uniform radiation profile. The outer balloon 12 in the Ishiwara et al. patent functions only to stabilize the device within and hold a thermal mass (liquid) against surrounding tissue so that it can be warmed or cooled by thermal conduction. There is no teaching or suggestion in the patent of how to provide a uniform radial absorbed dose profile of emissions emanating from the liquid radiation source 38. Moreover, given the banana shape of the Ishiwara device, the profile will be much different proximate the distal and proximal ends of the balloon 12 than in its central tissue contacting region. Thus, it cannot be said that applicants' invention, as claimed, is taught by or inherent in the Ishiwara '360 device.

Given the above mentioned differences, neither Claim 1 nor any of the remaining dependent claims is anticipated by the

Ishiwara et al. teachings. It is further submitted that the invention of Claim 1 is not rendered obvious from the teachings of the Ishiwara et al. patent.


While admittedly the present invention and the device described in the Ishiwara et al. patent have some points of similarity, i.e., both are catheters having an outer closed inflatable chamber and an inner spatial volume surrounded by the outer chamber and both are designed to provide radiation therapy to a tumor site, that is where the similarity ends. Applicants' invention is specifically designed to provide a uniform radial absorbed dose profile of the emissions from the particular chamber containing the radionuclide material so that occurrences of "hot spots" and/or "cold spots" are substantially eliminated. Hot spots can result in necrosis of healthy tissue, a condition to be avoided, while cold spots may mean that cancerous cells are not irradiated and killed. In one embodiment, uniformity of the radial absorbed profile is achieved by providing a spherical outer chamber which when inflated to contact the margins resulting following surgical removal of the tumor, a desired constant spacing will be maintained between the radiation source and the adjacent tissue structures. In a second embodiment, attention is paid to the spacing between the inner and outer radiation transparent walls so that it is constant over the entire surfaces of the two chambers. Given these important distinctions which are neither taught nor suggested by the Ishiwara reference, applicants' independent Claim 1, as amended,

is not made obvious from the prior art. In fact, it is proper to say that the Ishiwara et al. reference teaches away from applicants' invention given the elongate, cylindrical shape of the radiation source employed and the oblong-shaped outer balloon surrounding it.

In that Claim 1, as amended, has been shown to be patentable over the prior art, and because Claims 2-11 and 13 depend directly or indirectly from Claim 1, all of the claims remaining in the application are believed to be in condition for allowance and a Notice to that effect is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment in response to the Official Action of May 12, 1998 in application Serial No. 08/900,021 of inventors, Jeffery A. Williams et al., filed July 24, 1997, for "DOUBLE WALL BALLOON CATHETER FOR TREATMENT OF PROLIFERATIVE TISSUE" is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on September 1, 1998.

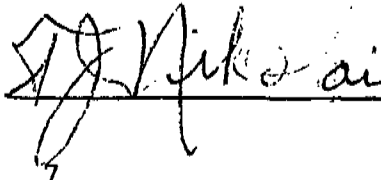
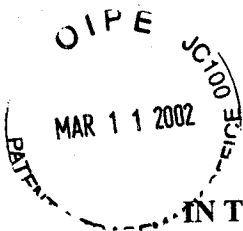


EXHIBIT J



COPY OF PAPERS
ORIGINALLY FILED

Docket No.: 101360-16
(PATENT)

#6/A (mai)
J.A.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Rance A. Winkler, et al.

Application No.: 09/464,727-7988

Group Art Unit: 3736

Filed: December 16, 1999

Examiner: J. Lacyk

For: ASYMMETRIC RADIATION DOSING
APPARATUS AND METHOD

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: 2/27/02

Signature:

(Ronald E. Cahill)

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AMENDMENT

Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Office Action dated October 31, 2001 (Paper No. 5), please amend the above-identified U.S. patent application by replacing all of the claims with the Clean Copy of All Pending Claims below. A Complete Set of Pending Claims With Markings to Show Amendments Made is attached to this Amendment following the signature page.

03/14/2002 00000029 09464727

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03/14/2002 00000029 09464727

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Application No.: 09/464,727-7988

Docket No.: 101360-16

Clean Copy of All Pending Claims

1. (Amended) An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves with respect to the apparatus volume.

2. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

A | a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

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5. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

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a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. (Amended) An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

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a radiation source disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume.

10. (Amended) The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

15. Canceled.

16. Canceled.

17. Canceled.

18. Canceled.

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19. Canceled.

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REMARKS/ARGUMENTS

Applicants appreciate the Examiner's indication that claims 2 through 7 define allowable subject matter. Applicants have amended claims 2, 5 and 6 to be independent claims including the recitations of the base claim and any intervening claims and to correct any rejections under 35 U.S.C. § 112, second paragraph. Applicants have also amended the preamble to read that the recited apparatus is a surgical apparatus for providing radiation treatment to target tissue. This amendment is supported in the opening paragraph of the Detailed Description of the Invention.

Applicants have amended independent claim 1 (from which claim 8 depends) and independent claim 9 (from which claims 10 to 14 depend, directly or ultimately) to better define the invention. Applicants have also amended claim 10 to recite that radio-opaque material is disposed *only* on a portion of the expandable surface. Applicants cancel claims 15 to 19 herein. Accordingly, claims 1 to 14 are now pending.

Claim Rejections Over McGrath

Claims 1 and 9 stand rejected as anticipated by McGrath (US 6,036,631) under 35 U.S.C. § 102(e). In particular, the Examiner states that "McGrath et al discloses a device for treating tissue having an expandable outer surface and a radiation source disposed within the expandable surface having a plurality of solid radiation sources (Fig. 2B). McGrath et al also teaches the use of shielding to absorb some of the radiation."

McGrath is directed to a device and method for treatment of cancerous tissue from a body conduit, i.e., interluminal treatment. By contrast, Applicants' apparatus is an interstitial brachytherapy apparatus, used to treat remaining proliferative tissue surrounding a surgical extraction site such as might be found in the treatment of brain or breast cancers. As a result of this difference in purpose, there are a number of key differences in structure between McGrath and claims 1 and 9.

For example, the expandable outer surface of claims 1 and 9 defines a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated. (See Page 7, lines 8 to 15.) Further, the radiation source is disposed completely within the expandable surface and is spaced apart from the apparatus volume. (See Page 8, line 23 to page 9 line 13, noting the

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advantages of providing the radiation source within the interstitial volume and spaced apart from the target tissue; See also each of FIGS. 1 and 3 through 9, showing the radiation sources disposed entirely within the expandable surface). Further with respect to claim 1, the radiation source is located and arranged within the expandable outer surface so as to create asymmetric radiation isodose curves with respect to the apparatus volume. (See Page 9, line 23 to page 10, line 7.) That is, the radiation source is arranged within the device so that asymmetric dosing appears at the apparatus volume, which is configured to correspond to the interstitial void created by surgical extraction of diseased tissue.

The device of McGrath is not configured for use interstitially, it is configured for use interluminally, with balloons provided only to hold its catheter within a lumen, or to dilate the lumen. Accordingly, the radiation source in McGrath is not located completely within any of the disclosed balloons, nor is it located and arranged to provide an asymmetric dose at an apparatus volume that conforms to an interstitial void. Rather, McGrath provides an x-ray tube 48 that slides within a catheter, or a plurality of radiation-emitting seeds 52 "essentially forming a linear source." (Column 5, lines 34 to 37.) Accordingly, McGrath lacks several of the features recited in claim 1.

McGrath also lacks the features recited in claim 8 which depends from claim 1. Claim 8 recites that the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth. That is, the expandable outer surface actually causes the interstitial void to take on the same shape as the apparatus volume so that, even for oddly shaped voids in soft tissue, the shape of the target tissue that is to receive the asymmetric radiation dose will be the same as for the apparatus volume, enabling precise delivery of prescription doses of radiation asymmetrically from Applicants' claimed configuration.

As described above, McGrath does not disclose, teach or suggest the configuration that is recited in claim 9 that is also recited in claim 1. In addition to the structure it recites in common with claim 1, claim 9 recites an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with

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respect to the apparatus volume. No portion of McGrath provides an outer expandable surface defining such an apparatus volume, and, while other configurations are referred to generically, the shielding that is provided by McGrath is simply a tubular shield that protects the bladder neck and sphincter. (See, Column 10, lines 7 to 39.) Nowhere does McGrath disclose, teach or suggest providing asymmetric shielding spaced apart from a radiation source so as to create predetermined asymmetric isodose curves with respect to an apparatus volume defined by the outer expandable surface.

Claim Rejections Over Ciezki in view of Apple

Claims 1 and 8 to 14 stand rejected as unpatentable over Ciezki (EP 0 867 200) in view of Apple (WO 99/33515) under 35 U.S.C. § 103. In particular, the Examiner states that:

Ciezki et al teaches a treatment device having a plurality of radiation sources disposed in a catheter. Ciezki et al also teaches the use of shielding or an attenuator made from a radio-opaque material i.e. tantalum. Ciezki et al teaches the claimed device except for the use of an inflatable balloon catheter or the specific use of barium as the shielding material. Apple et al teaches a radioactive treatment device that uses an inflatable balloon to place the catheter at the treatment site. . . . Therefore a modification of Ciezki et al such that the catheter includes an inflatable balloon would have been obvious to help in the placement and retention of the catheter at the treatment site;

The combination of Ciezki and Apple suffers from all of the same problems as McGrath does. Regarding claim 1, the Examiner recognizes that Ciezki does not provide an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated; and a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume. Apple does not fill in this missing teaching. Apple is directed to a catheter apparatus that is filled with a radioactive gas. The catheter can be used to treat restenosis after angioplasty, or it can treat malignancies. The "restenosis" configuration includes a number of balloons of the type generally used to hold a catheter in an artery; that is, interlumenally. None of these balloons define an apparatus volume within an interstitial void within which the radioactive source is completely placed. Even where Apple discloses a device for interstitial use (See, e.g., FIGS. 17 to 19), the radiation source completely fills the balloon and is not in a spaced apart relationship from the balloon as is recited in claim 1. Thus, even if a balloon from Apple were added to Ciezki, the configuration of claim

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1 would not result.

More significantly, neither Apple nor Ciezki nor their combination teaches asymmetric placement of a radiation source that is completely within an expandable surface defining an apparatus volume so as to result in asymmetric radiation isodose curves with respect to the apparatus volume. As described above and in the portions of the application cited above, Applicants' configuration provides significant advantages in the treatment of marginal proliferative tissue surrounding an interstitial void left by a surgical tumor resection. Accordingly, neither Ciezki nor Apple nor their combination renders the subject matter of claim 1 unpatentable to Applicants. Claim 8, which depends from claim 1, is further patentable over Ciezki and Apple because neither teaches or suggests the recitations of claim 8 for the same reasons as described above with respect to McGrath.

As described above, neither Ciezki nor Apple nor their combination discloses, teaches or suggests the configuration that is recited in claim 9 that is also recited in claim 1 – that is, an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated; and a radiation source disposed completely within and spaced apart from the expandable outer surface.

In addition to the structure it recites in common with claim 1, claim 9 recites an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume. No portion of Ciezki defines such an apparatus volume and the only embodiment of Apple that provides an apparatus volume (FIGS 17 to 19) does not include any shielding. Where Ciezki and Apple do provide shielding, it is to protect blood flowing through the apparatus as it irradiates an arterial wall. The disclosed shielding does not provide asymmetric radiation dosing with respect to an expandable outer surface defining an apparatus volume, because there is no such volume in these references. As described above and in the portions of the application cited above, Applicants' configuration with asymmetric shielding provides significant advantages in that it provides precise delivery of prescription doses of radiation asymmetrically about an interstitial void created by surgical resection of diseased tissue. Neither of these references, alone or

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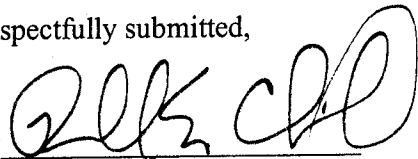
combined, teach or suggest a device that achieves this result.

Conclusion

For all of the foregoing reasons, Applicants request that the Examiner reconsider the application and allow each of claims 1 to 14 to issue. If the Examiner believes that an interview would facilitate the resolution of any outstanding issues, the Examiner is kindly requested to contact the undersigned.

Dated: 2/27/02

Respectfully submitted,

By 

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Application No.: 09/464,727-7988

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Complete Set of Pending Claims With Markings to Show Amendments Made

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining [an] a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source [replaceably disposable] disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source [comprising a plurality of solid radiation sources arranged] further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves [within the target tissue] with respect to the apparatus volume.

2. [The apparatus of claim 1, wherein a] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources [are] being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the

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catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. [The apparatus of claim 1,] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. [The apparatus of claim 1, wherein] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources [are] being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

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an expandable outer surface having a base and defining [an] a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source [replaceably disposable] disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves [within the target tissue] with respect to the apparatus volume.

10. The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.
11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.
12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.
13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.
14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.
15. Canceled.
16. Canceled.
17. Canceled.
18. Canceled.

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19. Canceled.

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Attorneys for Plaintiffs
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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

HOLOGIC, INC., CYTYC CORPORATION,
and HOLOGIC L.P.,

Plaintiffs,

vs.

SENORX, INC.,

Defendant.

AND RELATED COUNTERCLAIMS.

Case No. C08 00133 RMW (RS)

MANUAL FILING NOTICE

Date: June 25, 2008
Time: To Be Set
Room: Courtroom 6, 4th Floor
Judge: Hon Ronald M. Whyte

1 Regarding: Exhibits E and G to the Declaration of Katharine L. Altemus in Support of
2 Plaintiffs' Opening Claim Construction Brief

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11 By: /s/
12 Katharine L. Altemus

14 HOWREY LLP
15 Attorneys for Plaintiffs
16 Hologic, Inc., Cytoc Corporation,
and Hologic L.P.